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WHAT LIES BEYOND EGFR, ALK AND ROS1 TARGETED THERAPIES?

Melissa L. Johnson, MD
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MELISSA JOHNSON, MD

NOVEL CARCINOGENIC PATHWAYS AND NOVEL THERAPIES FOR METASTATIC NSCLC (EXCEPT EGFR, ALK, ROS-1)

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

GRANT/RESEARCH SUPPORT: BERGENBIO, LILLY, EMD SERONO, JANSSEN, MIRATI THERAPEUTICS, GENMAP, PFIZER, ASTRAZENECA, GENENTECH, STEMCENTRIX, NOVARTIS, CHECKPOINT THERAPEUTICS, ARRAY BIOPHARMA, REGENERON, APEXIGEN, ABBVIE, TARVEDA, ADAPTIMMUNE, SYNDAX, NEOVIA, BIPI, SANOFI, HENGRUI THERAPEUTICS, INC., MERCK, DAIICHI-SANKYO, LYCERA, G1 THERAPEUTICS, DYNAVAX
CONSULTANT: ASTELLAS, OTSUKA PHARMACEUTICALS (SPOUSE), GENENTECH, CELGENE, BIPI, SANOFI, MIRATI, LOXO

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

The Medical Educator Consortium

13th Annual New Orleans Summer Cancer Meeting
July 20-22, 2018

OVERVIEW—"NEW" MOLECULAR SUBTYPES IN NSCLC

- Precision medicine focuses attention on broad molecular testing
- Advances in targeted therapies in 2018:
  - RET
  - MET
  - EGFR/HER2 EXON 20 insertion
  - NTRK
  - BRAF
- Interplay between targeted therapies and IO

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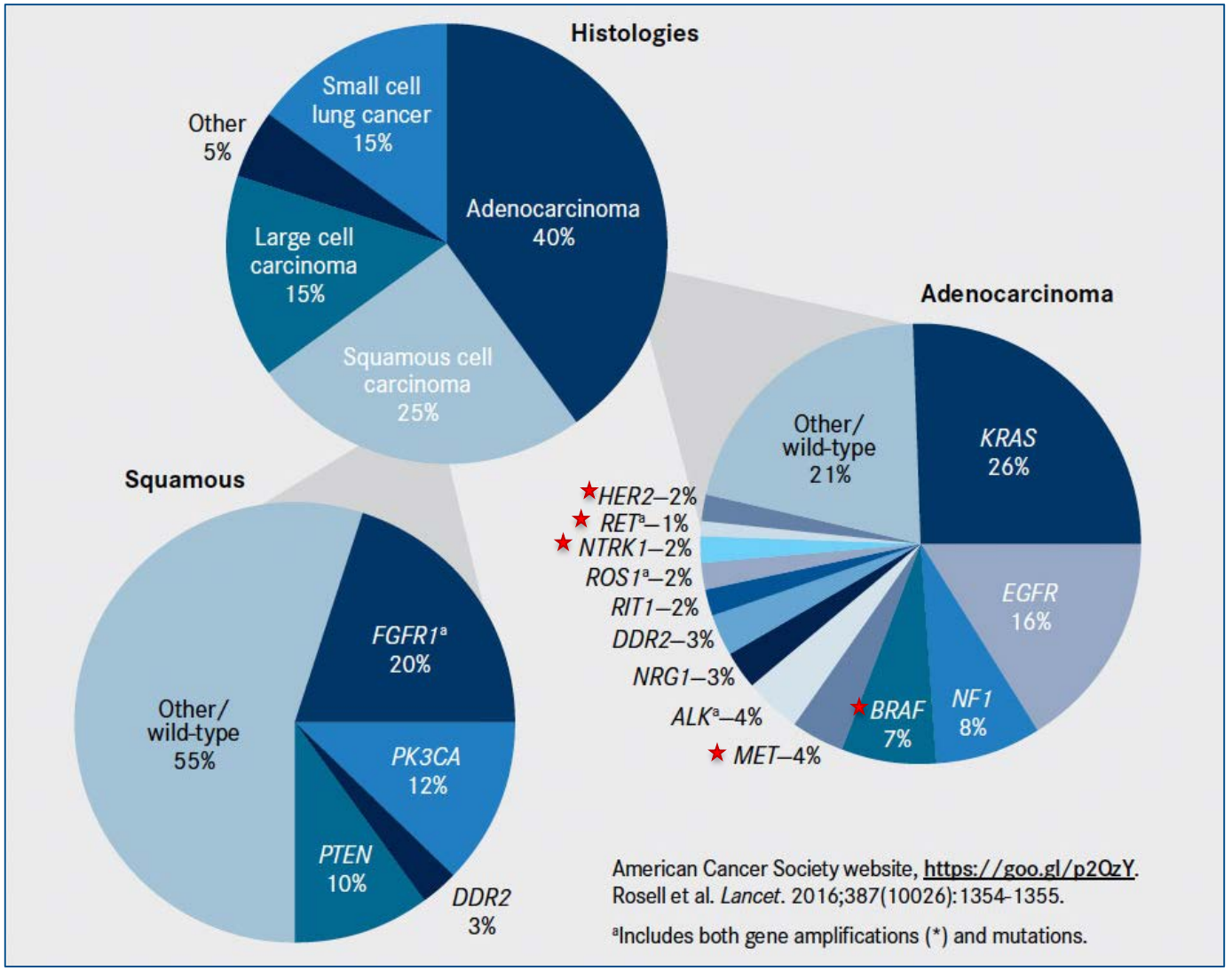
LUNG CANCER SUBTYPES AND MOLECULAR DRIVERS



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COMPREHENSIVE MOLECULAR PROFILING IN THE NEWS

DRUG DISCOVERY & DEVELOPMENT

FDA Finalizes Guidances for Next-Generation Sequencing Tests

Fri, 04/13/2018 - 9:58am by FDA

HEALTHCARE FINANCE

MAR 16 | MORE ON ANALYTICS

CMS approves Next Generation Sequencing for cancer patients

The FoundationOne CDx test is the first breakthrough-designated in vitro diagnostic test and can detect genetic mutations in 324 genes.

Susan Morse, *Senior Editor*

The Centers for Medicare and Medicaid Services has finalized coverage of Next Generation Sequencing for cancer patients.

FOR THE ONCOLOGY SPECIALIST

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VOL. 19 | NO. 4 | FEBRUARY 2018

NGS Testing Hits Clinical Practice

JOURNAL OF CLINICAL PATHWAYS

THE FOUNDATION OF VALUE-BASED CARE

Next-Generation Sequencing Proves Cost-Effective in Metastatic NSCLC

05/17/18

An economic model comparing different types of genetic testing in metastatic non-small cell lung cancer (NSCLC) showed that next-generation sequencing (NGS) is more cost-effective than testing for one or a limited number of genes at a given time.

Targeted Oncology

Next-Generation Sequencing for Metastatic NSCLC Associated With Substantial Cost Savings

Angelica Welch

Published Online:5:05 PM, Wed May 16, 2018

Forbes

MAR 6, 2018 @ 10:30 AM 9,474

All Cancer Patients Should Have Access To Genomic Testing

Days after Thanksgiving, the FDA approved Foundation Medicine's comprehensive genetic test for evaluating cancer. The idea—and practice—of testing tumors for specific DNA or protein abnormalities is not new. Previously, the agency listed several dozen approved companion diagnostic tests; these earlier tools check one or a few molecules to inform the cancer subtype, prognosis, and likelihood of response to treatments.

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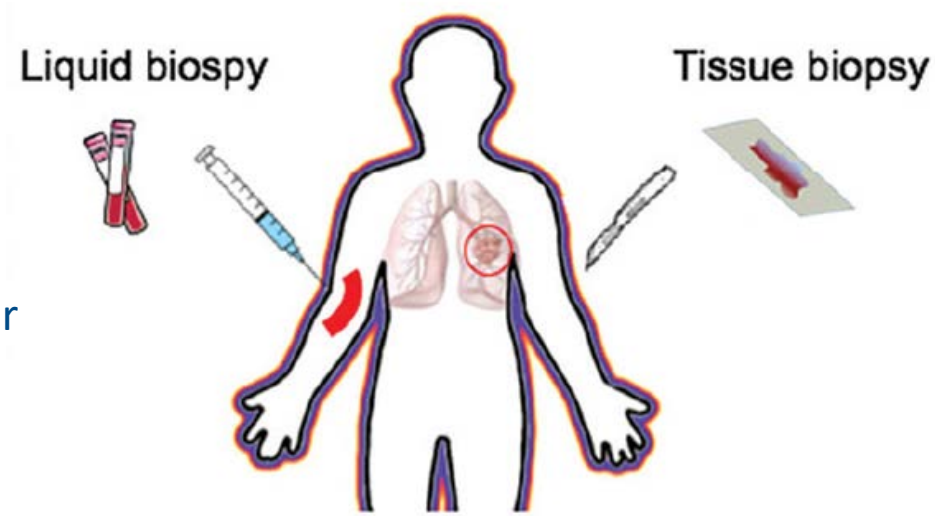
COMPREHENSIVE GENOMIC PROFILING—LIQUID OR TISSUE

Liquid Biopsy

- Non-invasive blood test
- “Summation” of tumor heterogeneity
- Potential for periodic monitoring for response or resistance
- Speed



Tissue Biopsy

- Gold standard
- Invasive procedure
- Tissue accessibility
- Limited to biopsied tissue only
- Clinical complications
- Cost
- Time

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NGS TESTING IN NSCLC SAVES CMS PAYER $1.4M TO $2.1M, AND PROPORTIONATE COMMERCIAL PAYER SAVINGS, WITH FASTER TURN AROUND TIME

Total payer test costs:

- **CMS** (2,066 patients): $2,190,499 (NGS); $3,721,368 (Sequential); $3,584,177 (Exclusionary); and $4,331,295 (Hotspot panel).
- Commercial (156 patients): $620,369 (NGS); $747,771 (Sequential); $624,178 (Exclusionary); and $871,211 (Hotspot panel).

Time to appropriate therapy:

- With NGS and Hotspot panel, patients initiate appropriate therapy 2.8 and 2.7 weeks faster that sequential and exclusionary, respectively.
- Patients with alterations with FDA approved therapies: NGS identifies 2.3% > sequential, and 5.9% > exclusionary
- Patients with alterations without FDA approved therapies: NGS identifies 43.7% > sequential and 32.2% > exclusionary, and 36.1% > Hotspot panel testing.
- If 50% instead of 25% of NSCLC patients are NGS tested payer save $492,250 (CMS, n=2,066) and $52,421 (commercial, n=156).

Figure 2: Cost savings associated with NGS use vs. other strategies for CMS Medicare perspective (N=2,066)

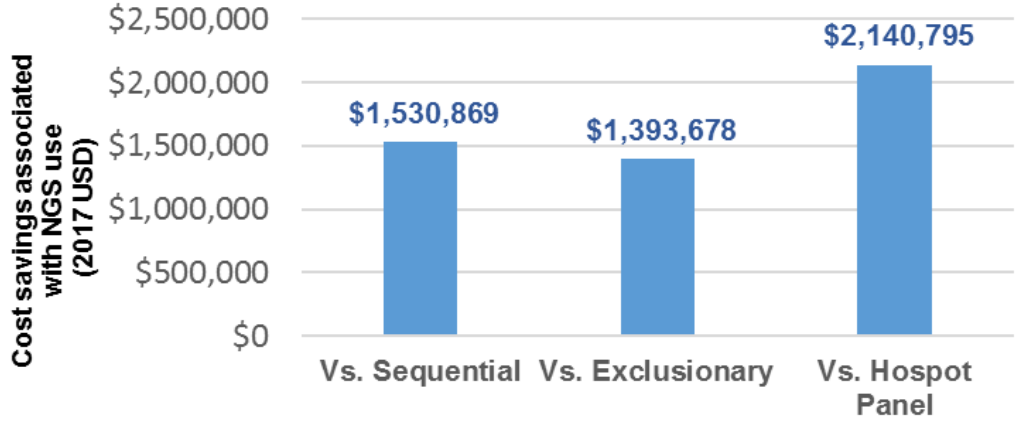
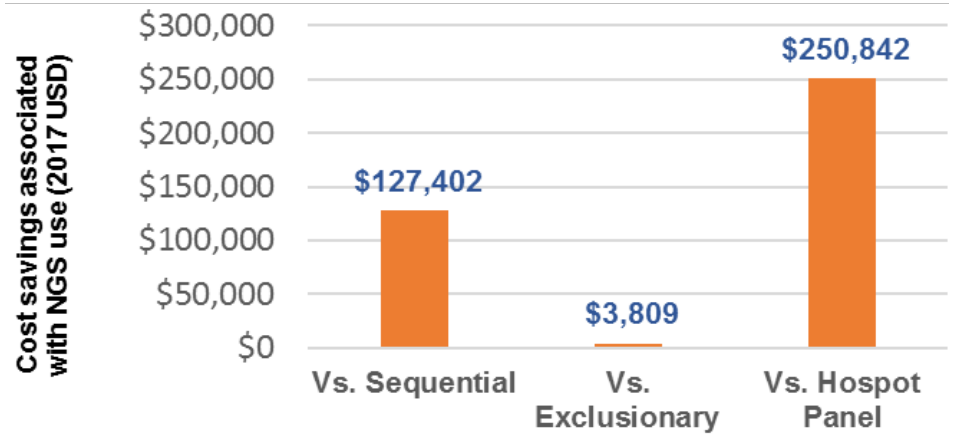


Figure 3: Cost savings associated with NGS use vs. other strategies for commercial payer perspective (N=156)



CONCLUSION: Upfront NGS testing in metastatic NSCLC patients yields substantial savings for US payers whilst promptly enabling the identification of the right patient for right treatment. NGS testing ought to be used more widely in metastatic NSCLC patients.

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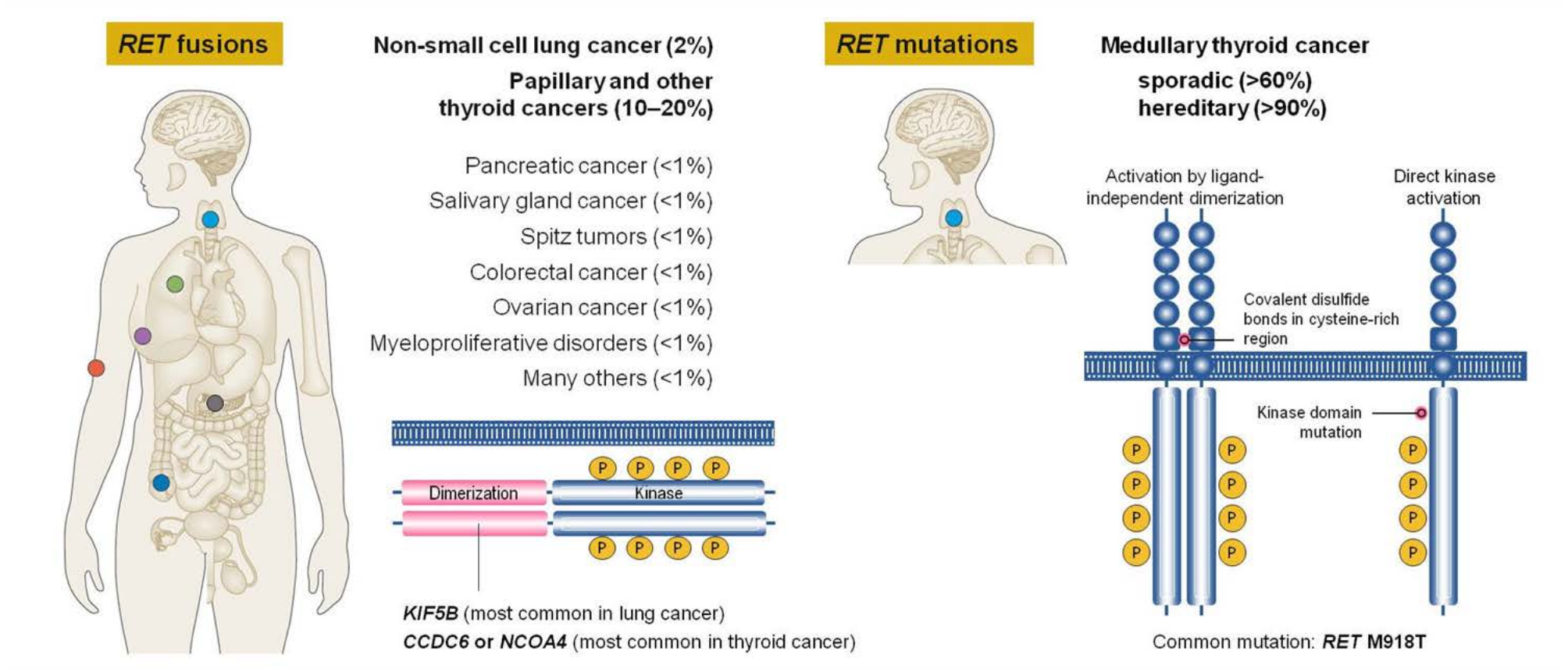
Pennell et al. pASCO 2018

RET [REARRANGED DURING TRANSFECTION] ACTIVATED BY TWO MAJOR MECHANISMS

- In NSCLC, RET fusions are present in 1% to 2% of cases.
- Increases substantially in never-smokers with lung adenocarcinomas lacking other known driver oncogenes.



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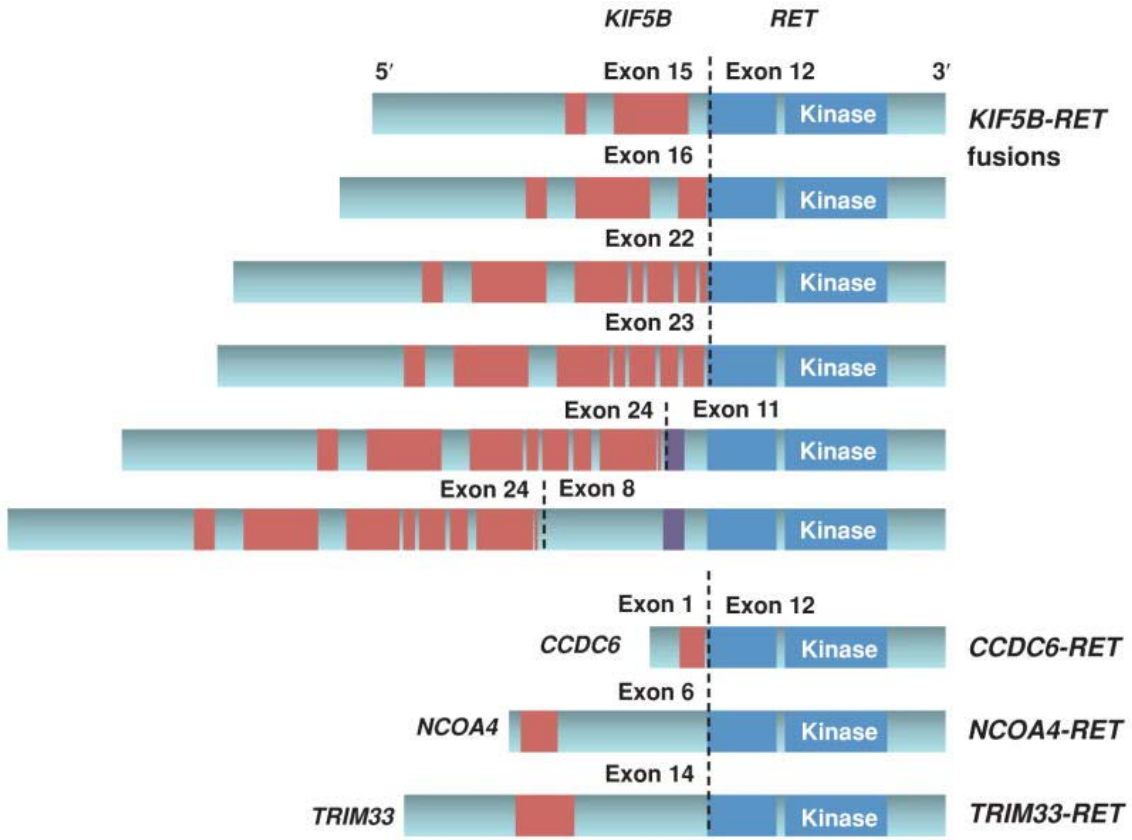
Drilon A. et al. 2018 ASCO Annual Meeting

RET FUSIONS



- *RET* fusions reported in the literature are depicted including major recurrent *KIF5B–RET* fusions, *CCDC6–RET*, *NCOA4–RET* and the novel *TRIM33–RET*.
- All fusions encode an intact RET kinase domain as shown in blue. Regions encoding coiled-coil domains that mediate dimerization are shown in red (the N-terminal *NCOA4* coiled-coil domain is not well defined).
- Part of the RET transmembrane domain encoded by *RET* exon 11 is shown in purple.

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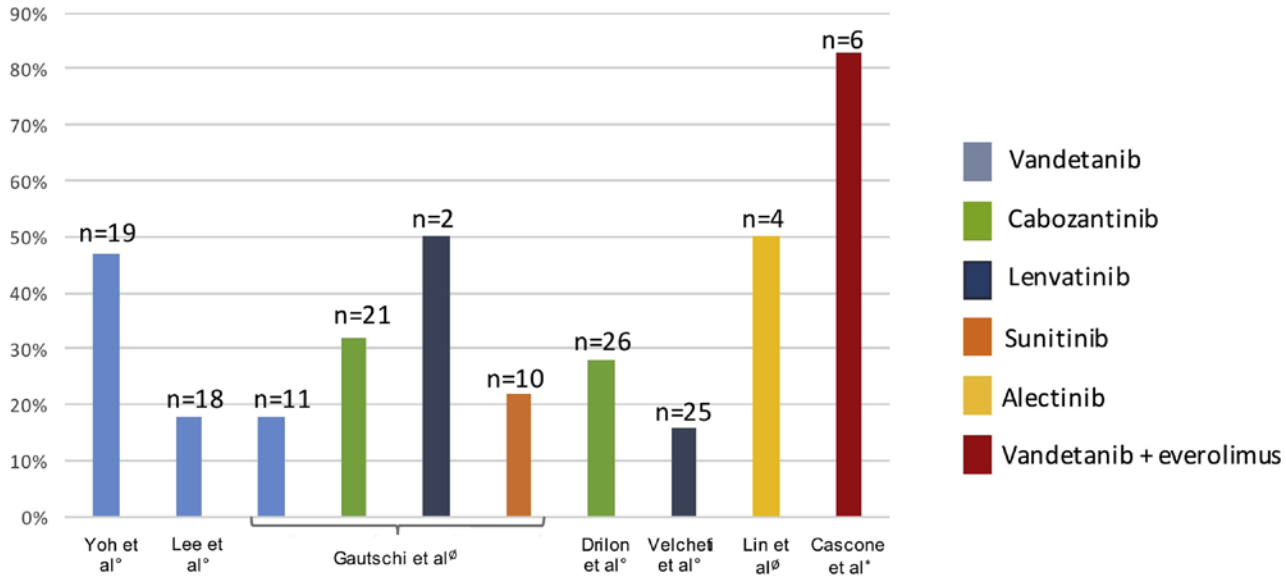
Drilon A. et al. Cancer Discovery 2013;3:630-635

RET INHIBITION IN NSCLC



Type of RET Inhibitor	Study	No. of Patients	ORR	mPFS (mo)	mOS (mo)
Vandetanib	Yoh et al. (2016) LURET	19	47%	4.7	11.1
	Lee et al. (2017)	18	18%	4.5	11.6
	Gautschi et al. (2017) GLORY	11	18%	2.9	10.2
	Platt et al. (2015)	3	0%	NA	NA
Cabozantinib	Drilon et al. (2016)	26	28%	5.5	9.9
	Gautschi et al. (2017) GLORY	21	32%	3.6	4.9
Lenvatinib	Velcheti et al. (2016)	25	16%	7.3	NA
	Gautschi et al. (2017) GLORY	2	50%	NA	NA
Sunitinib	Gautschi et al. (2017) GLORY	10	22%	2.2	6.8
Alectinib	Lin et al. (2016)	4	50%	NA	NA
	Gautschi et al. (2017) GLORY	2	0%	NA	NA
Sorafenib	Gautschi et al. (2017) GLORY	2	0%	NA	NA
	Horiike et al. (2016)	3	0%	NA	NA
Ponatinib	Gautschi et al. (2017) GLORY	2	0%	NA	NA
Vandetanib + everolimus	Cascone et al. (2016)	6	83%	NA	NA

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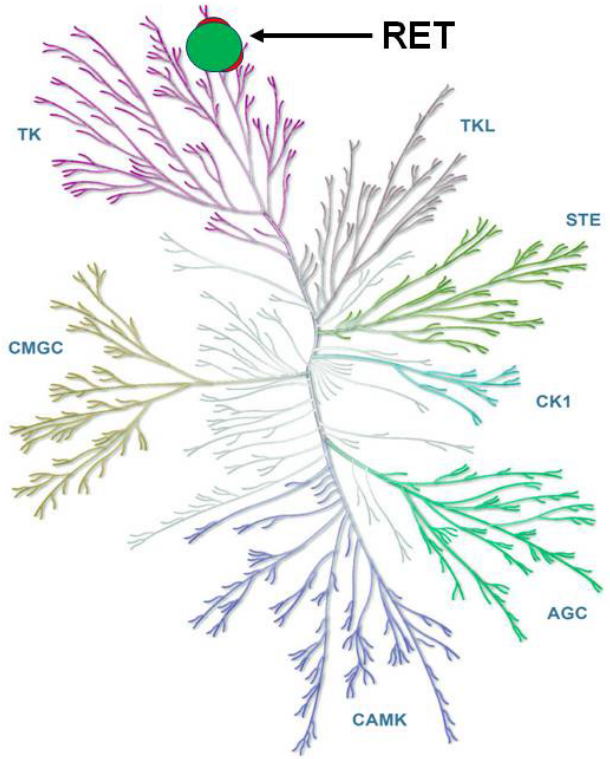
Ferrara et al. J Thorac Oncol. 2018 Jan; 13(1):27-45.

RET: LOXO-292

- LOXO-292 is a potent and selective RET inhibitor

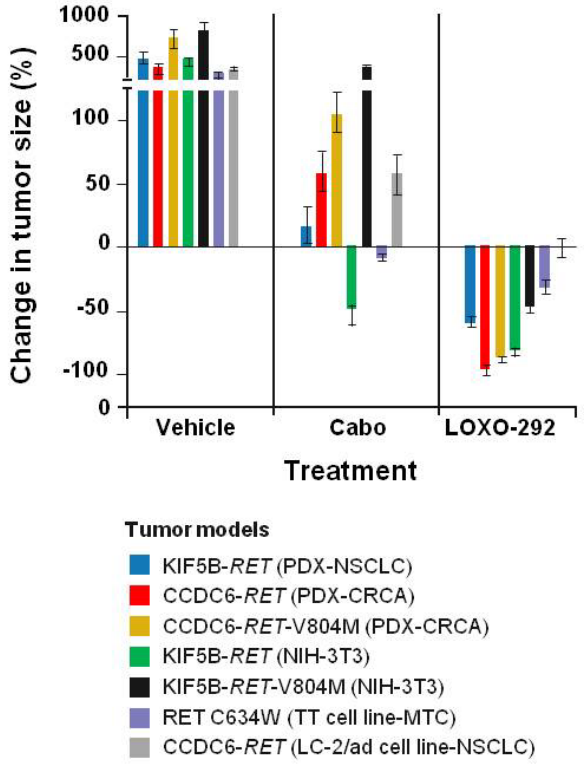
Kinome selectivity

Highly selective for RET



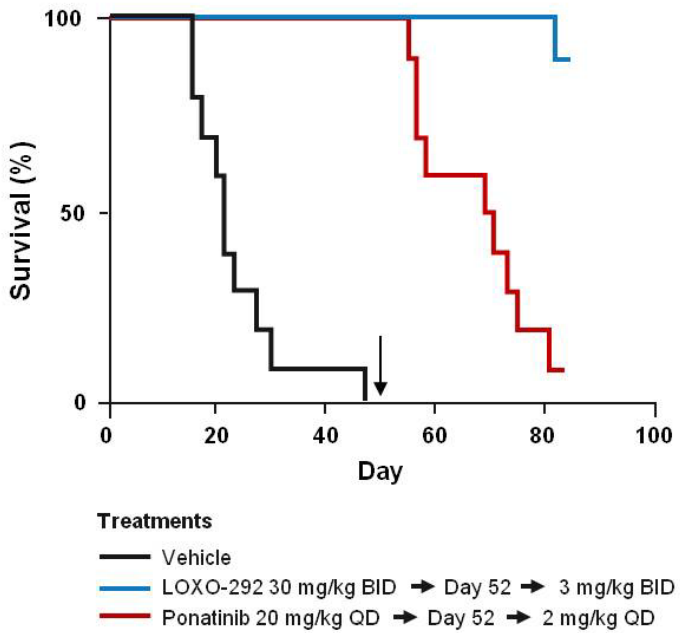
Xenograft models

Multiple fusions/mutations/histologies



Orthotopic brain model

CCDC6-RET orthotopic brain PDX



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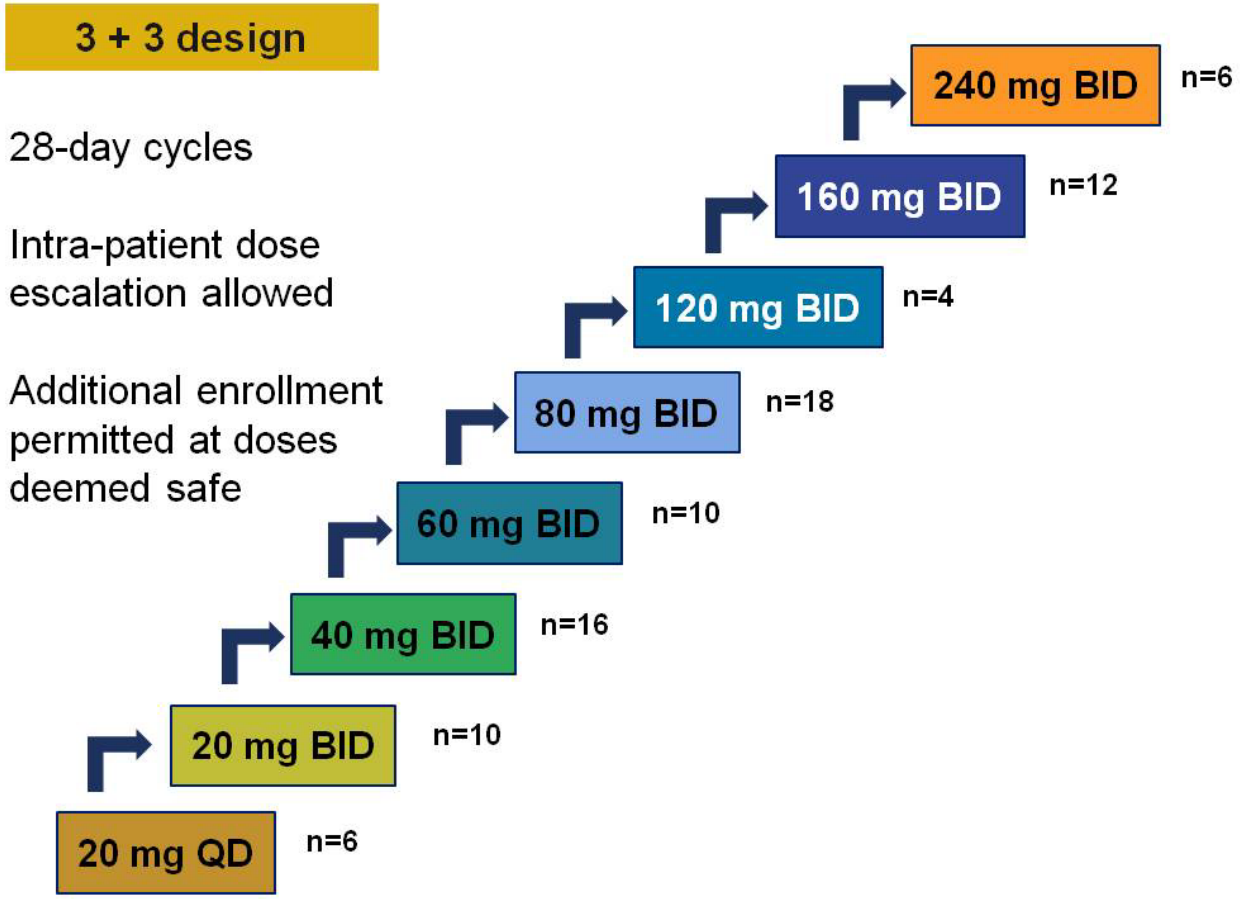
LIBRETTO-001- PHASE 1 DOSE ESCALATION WITH LOXO-292

Eligibility

- Age ≥12 years
- ECOG 0–2
- Patients with locally advanced or metastatic solid tumors refractory or intolerant to standard therapy
- Any number of prior therapies
- *RET* alteration not required initially ('triggered' by adequate PK)

Key endpoints

- Determine MTD or recommended dose
- Safety/tolerability
- PK
- Overall response rate (RECIST v1.1)
- Duration of response



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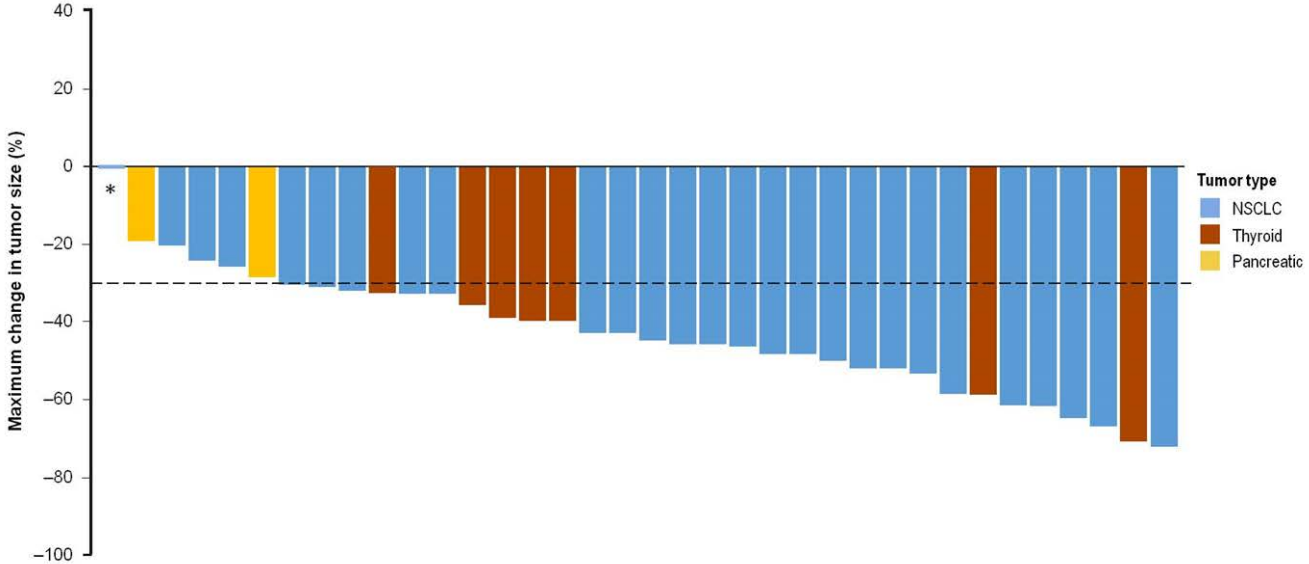
CLINICAL ACTIVITY OF LOXO-292 IN RET-ALTERED CANCERS

	RET fusion-positive cancers			*RET*-mutant MTC	No known activating *RET* alteration
	All	NSCLC	Other[1]		
Enrolled	49	38	11	29	4
Eligible for response evaluation[2]	39	30	9	22	3
Overall Response Rate (95% CI)[3]	**77% (61% – 89%)**	**77% (58% – 90%)**	**78% (40% – 97%)**	**45% (24% – 68%)**	**0% (0% – 71%)**
Confirmed Overall Response Rate[3,4]	74%	74%	71%	33%	0%
CR	–	–	–	1	–
uCR[5]	–	–	–	1	–
PR	25	20	5	5	–
uPR[5]	5	3	2	3	–
SD	6	4	2	9	2
PD	–	–	–	2	1
Not evaluable[6]	3	3	–	1	–

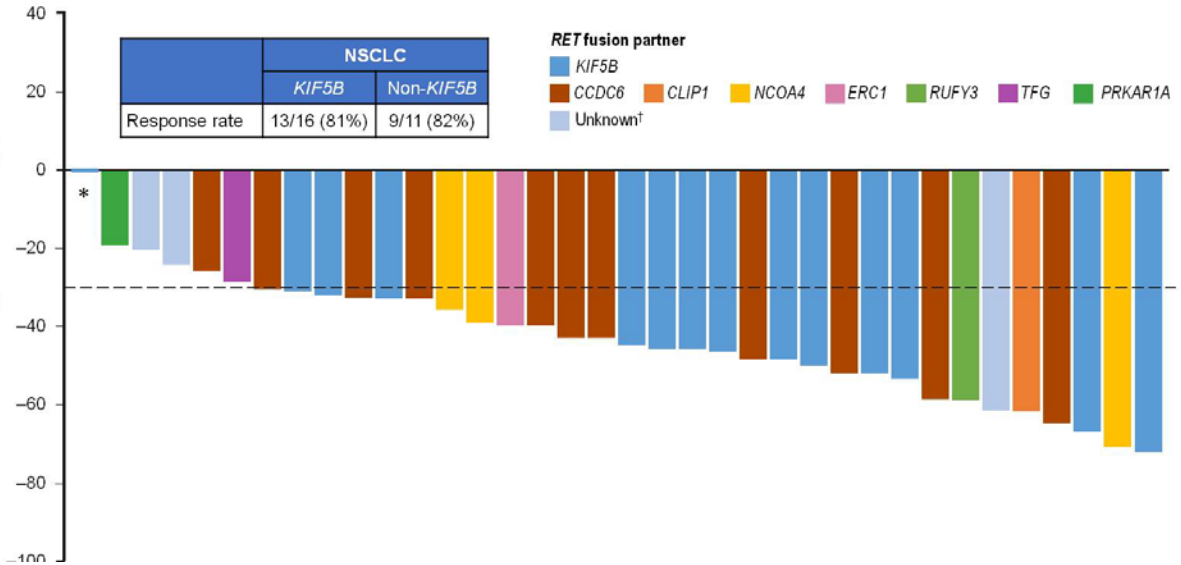
1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate, Confirmed overall response rate: all *RET* fusion-positive (30/39, 25/34), *RET* fusion-positive NSCLC (23/30, 20/27), *RET* fusion-positive other (7/9, 5/7), *RET*-mutant MTC (10/22, 6/18). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.

EFFICACY OF LOXO-292

RET FUSION-POSITIVE CANCERS



ACROSS RET FUSION PARTERS



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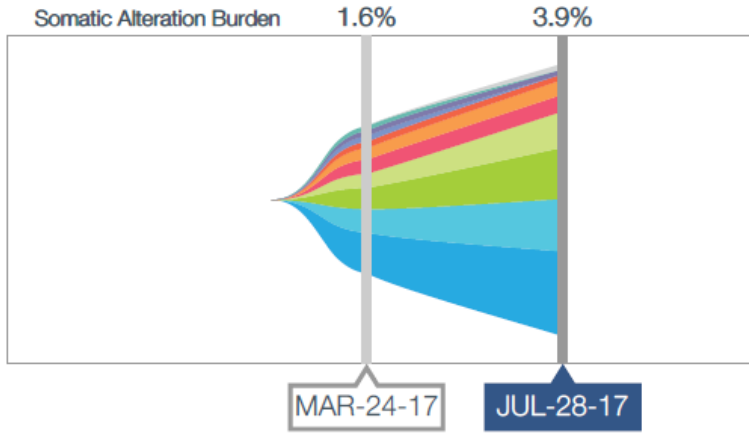
73 YO M NEVER-SMOKER ATTORNEY S/P CHEMORADIATION, PEMBROLIZUMAB AND PRIOR RET INHIBITOR



Alteration		Mutation Trend	% cfDNA or Amplification	FDA Approved in Indication *see page 4*	Available for Use in Other Indications *see page 4*	Clinical Drug Trials *see page 12*
Relevant for Therapy Selection						
APC	*S874**	100 50 5 0.5 ND	2.2	None	Celecoxib	Trials Available
RET	*KIF5B-RET fusion*	100 50 5 0.5 ND	1.4	None	Cabozantinib, Lenvatinib, Ponatinib, Regorafenib, Sorafenib, More drugs available	Trials Available
TP53	*Y220C*	100 50 5 0.5 ND	0.5	None	None	Trials Available
	I251M	100 50 5 0.5 ND	0.1	None	None	Trials Available
	H178P	100 50 5 0.5 ND	0.1	None	None	Trials Available
	Splice Site SNV	100 50 5 0.5 ND	0.1	None	None	Trials Available
Additional Alterations Detected						
SMAD4	*Q334**	100 50 5 0.5 ND	3.9	None	None	None
RET	*RET-KIF5B fusion*	100 50 5 0.5 ND	2.1	None	None	None
EGFR	*T431*	100 50 5 0.5 ND	0.5	The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.		
TP53	*R175H*	100 50 5 0.5 ND	ND			

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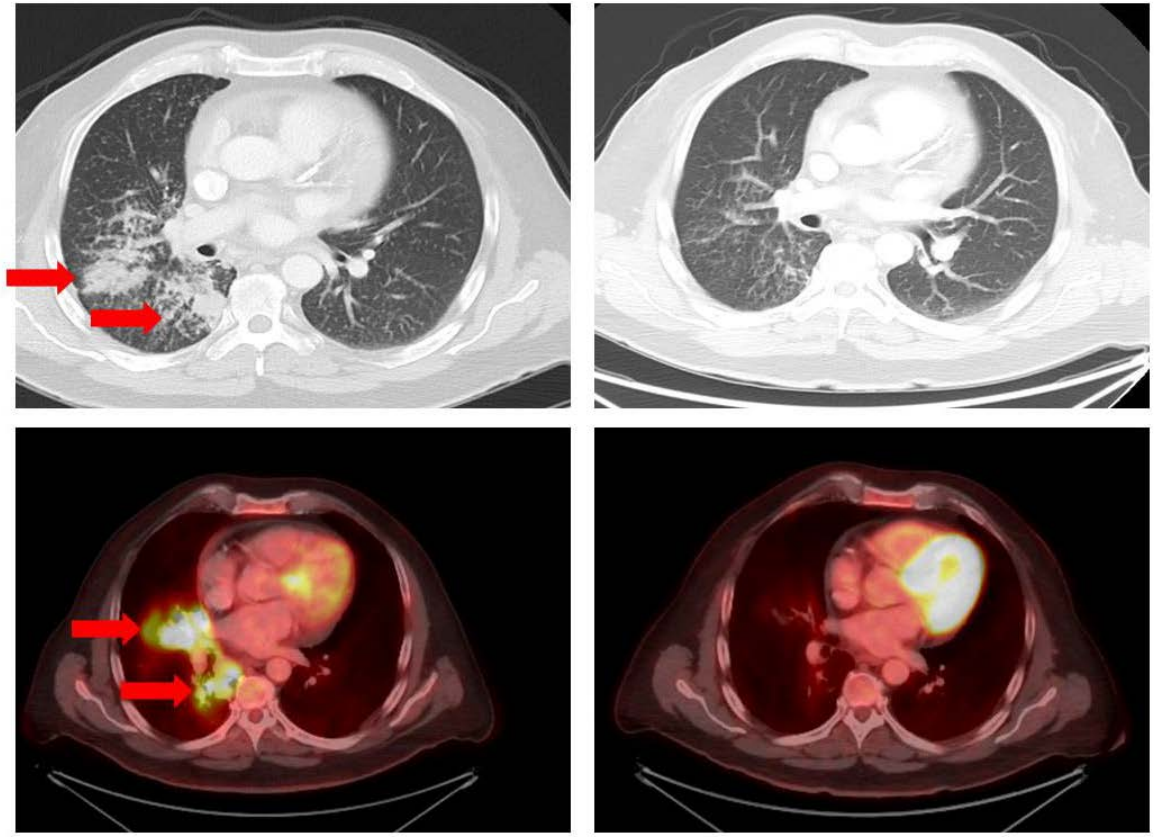
KIF5B-RET FUSION-POSITIVE NSCLC RESPONSE TO LOXO-292



- Initiated LOXO-292 at 80 mg BID, currently 160 mg BID (escalated at C4D1)
- Rapid improvement in shortness of breath and cough within a few days
- RECIST PR observed at his first response assessment at C2D1, confirmed at C3D1 (maximum tumor reduction-67%)
- Remains in response and on study in month 4

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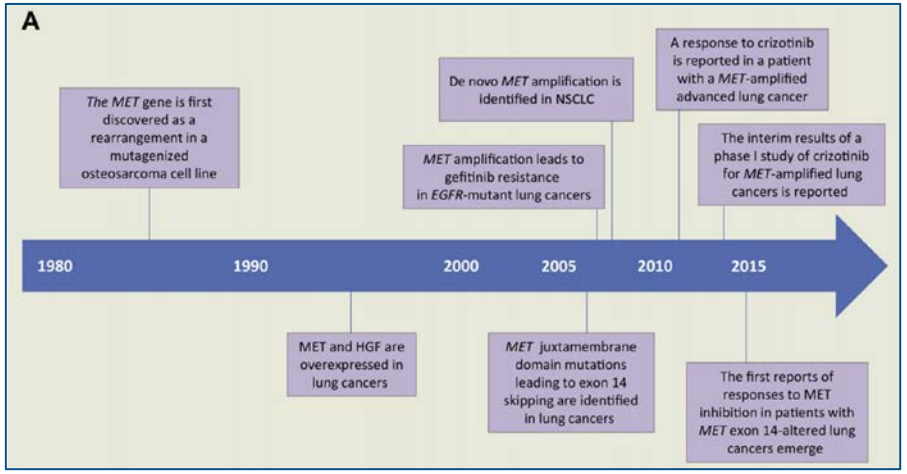
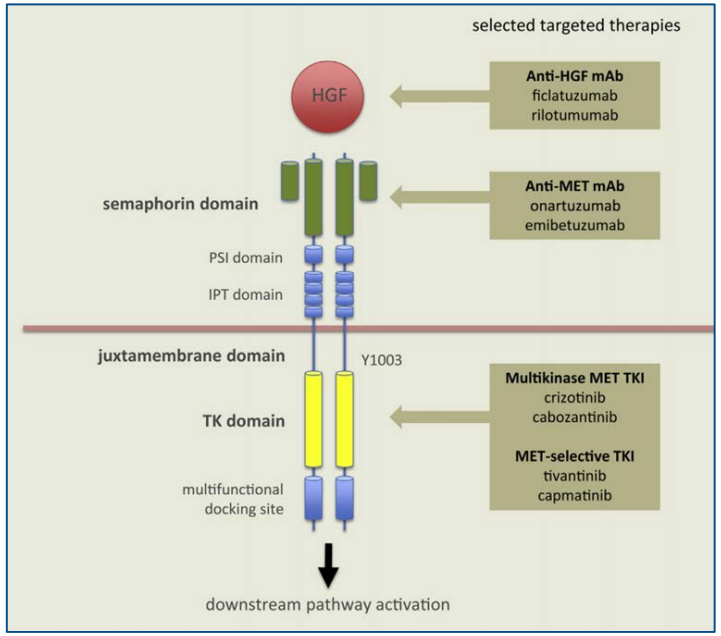
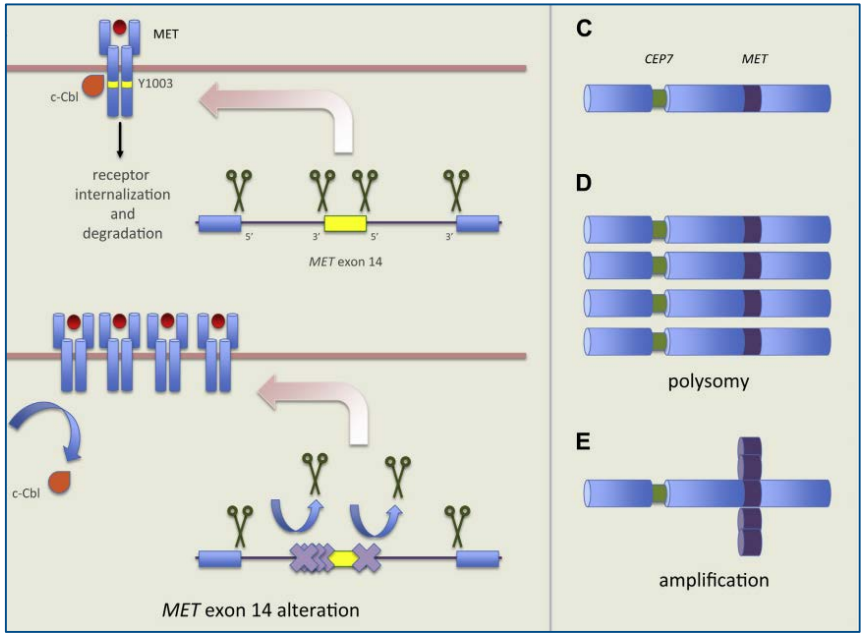
MET: MESENCHYMAL EPITHELIAL TRANSITION FACTOR RECEPTOR

- MET Alterations: MET exon 14 skipping mutations and MET amplification







Drilon, et al. J Thorac Oncol. 2017 Jan;12(1):15-26.

Impact of MET inhibitors on survival among patients with *MET* exon 14 mutant non-small cell lung cancer

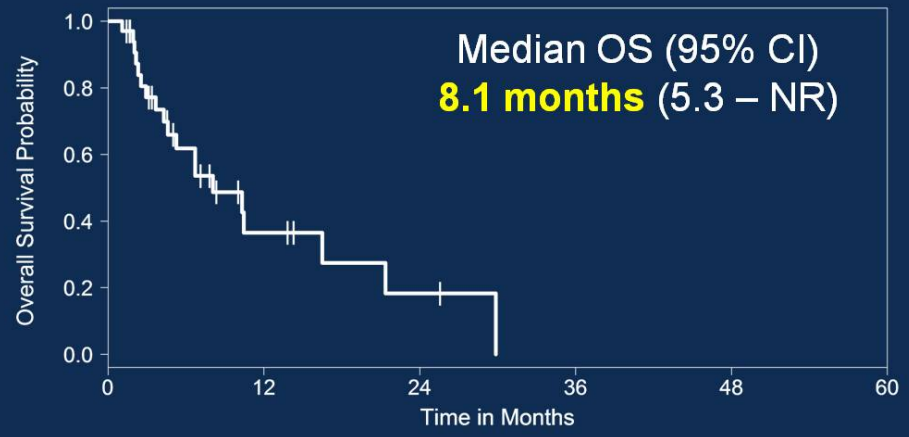
Mark M. Awad,[1] Giulia C. Leonardi,[1] Sasha Kravets,[1] Suzanne E. Dahlberg,[1] Alexander Drilon,[2] Sinead A. Noonan,[3] D. Ross Camidge,[3] Sai-Hong Ignatius Ou,[4] Daniel B. Costa,[5] Shirish M. Gadgeel,[6] Conor E. Steuer,[7] Patrick M. Forde,[8] Viola W. Zhu,[9] Yoko Fukuda,[10] Jeffrey W. Clark,[11] Pasi A. Jänne,[1] Tony Mok,[12] Lynette M. Sholl,[13] Rebecca S. Heist[11]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]University of Colorado, Aurora, CO; [4]University of California Irvine School of Medicine, Orange, CA; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Karmanos Cancer Institute, Detroit, MI; [7]Winship Cancer Institute, Atlanta, GA; [8]Johns Hopkins Kimmel Cancer Center, Baltimore, MD; [9]University of California San Francisco, Fresno, CA; [10]Frisbie Memorial Hospital, Rochester, NH; [11]Massachusetts General Hospital Cancer Center, Boston, MA; [12]Chinese University of Hong Kong, Hong Kong, China; [13]Brigham and Women's Hospital, Boston, MA.

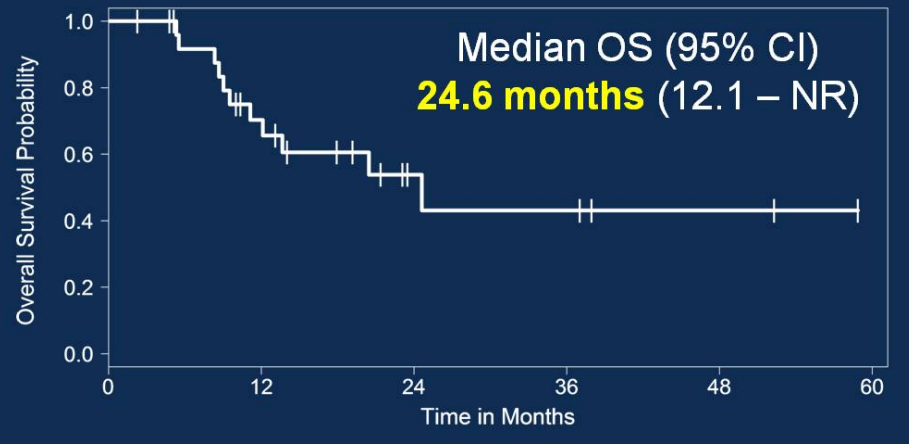
Clinical Science Symposium: Old Targets, New Drugs: HER2 and MET, June 4, 2017, 8:36 AM, Abstract #8511

Overall survival from date of stage IV diagnosis

Never received
a MET TKI
N = 34



Received
a MET TKI
N = 27



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Tepotinib in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring *MET* Exon 14-Skipping Mutations: Phase II Trial

E. Felip[1], L. Horn[2], J.D. Patel[3], H. Sakai[4], J. Scheele[5], R. Bruns[5], P.K. Paik[6], on behalf of the VISION Study Group

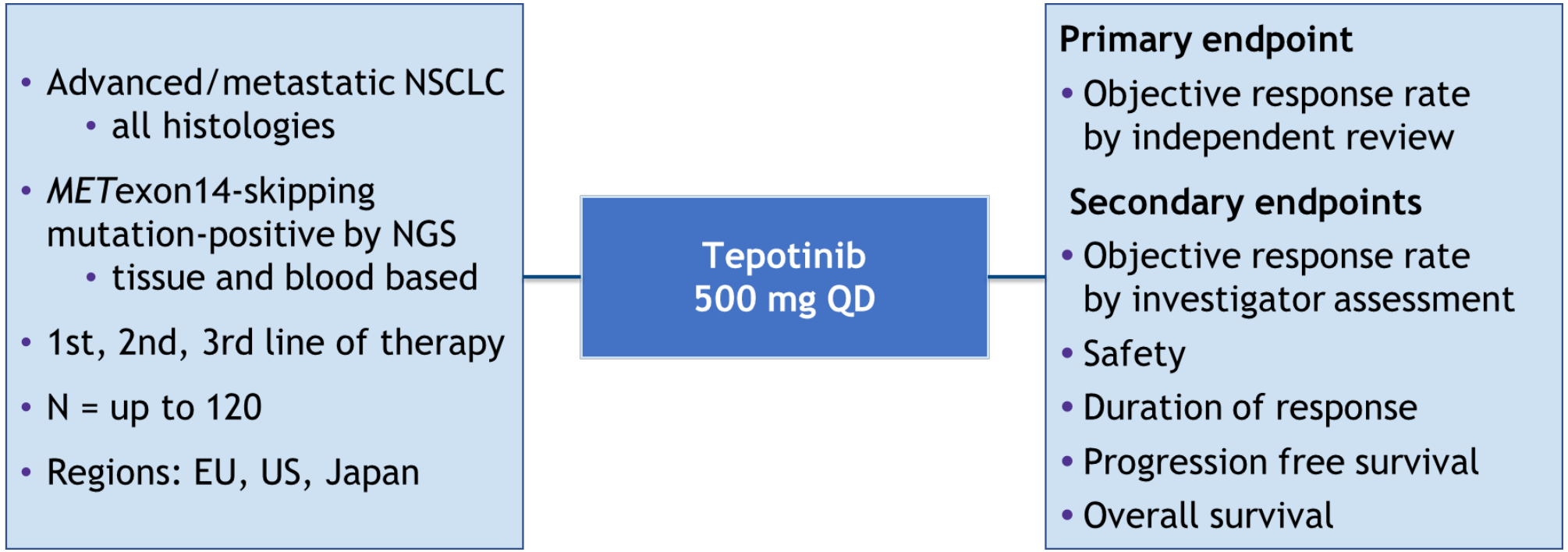
[1]Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Thoracic Oncology Program, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]Section of Pulmonary Medicine, University of Chicago Medical Center, Chicago, IL, USA; [4]Department of Respiratory Medicine, Saitama Cancer Center, Saitama, Japan; [5]Merck KGaA, Darmstadt, Germany; [6]Memorial Sloan Kettering Cancer Center, New York, USA

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

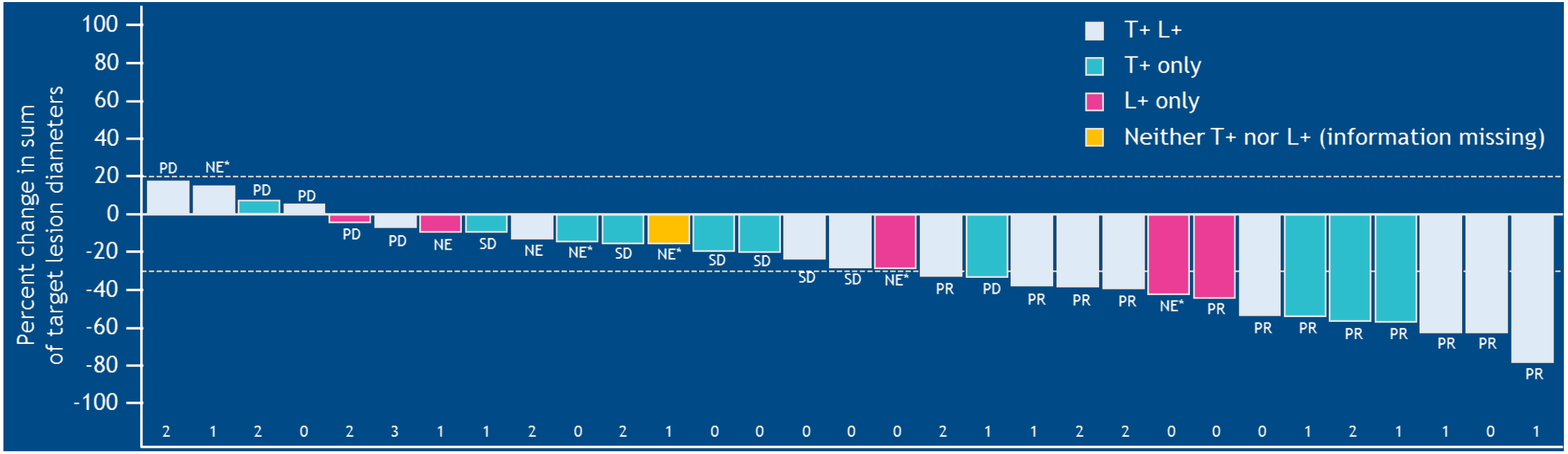
PRESENTED BY: Dr E. Felip

VISION: A PHASE II, SINGLE-ARM TRIAL TO INVESTIGATE TEPOTINIB IN ADVANCED NSCLC WITH *MET* EXON14-SKIPPING ALTERATIONS

- Single-arm, open-label, Phase II trial conducted at ~90 sites in Belgium, France, Germany, Italy, Japan, Poland, Spain, and the USA



EFFICACY: CHANGE IN SUM OF TARGET LESION DIAMETER: (INDEPENDENT REVIEW)



n=31. Seven patients were excluded due to baseline/on-treatment measurement not being available.
BOR displayed at the end of the bar.
NE*, BOR non-evaluable where ongoing patient has not had 2 post-baseline tumor assessments.
BOR, best overall response; CR, complete response; L, liquid biopsy; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.

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MET AMPLIFICATIONS: CRIZOTINIB IN PATIENTS WITH MET-AMPLIFIED NSCLC

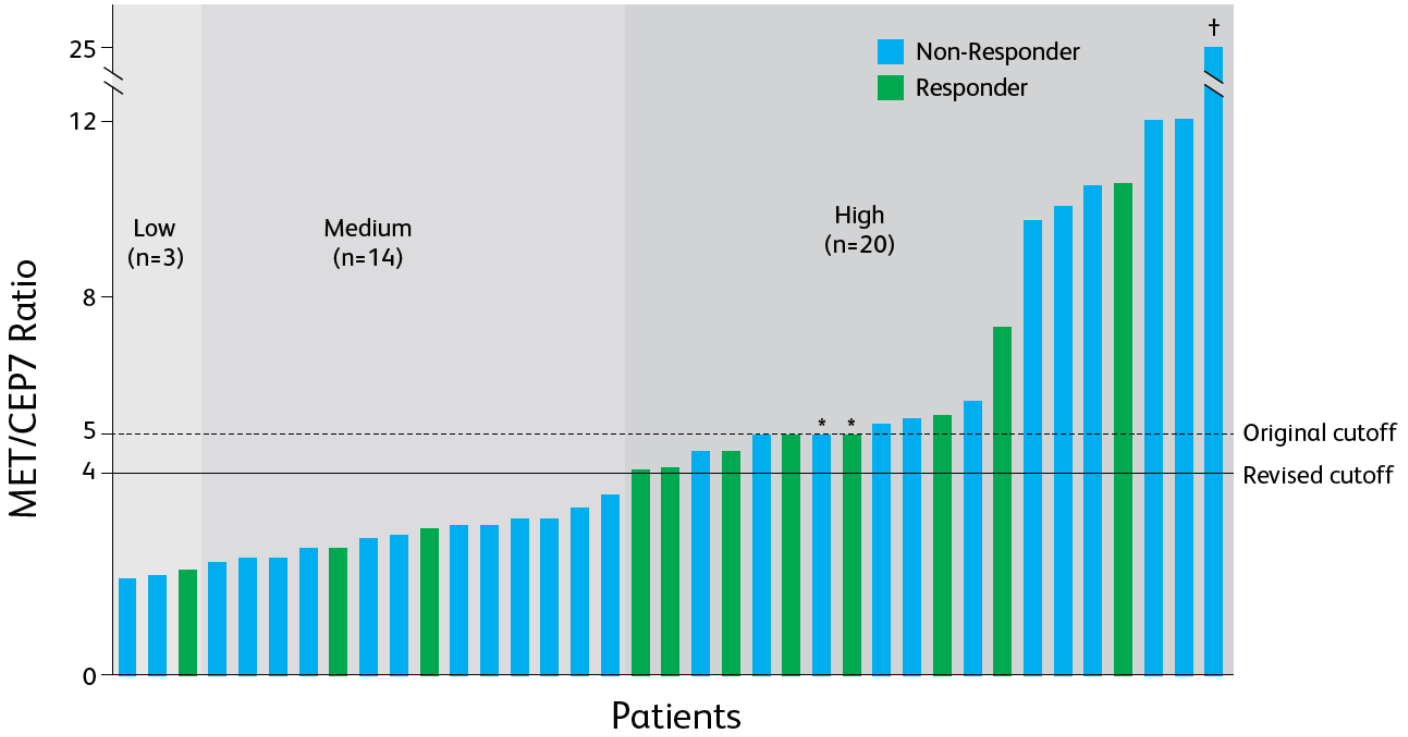
9062

Crizotinib in Patients With MET-Amplified Non-Small Cell Lung Cancer: Updated Safety and Efficacy Findings From a Phase 1 Trial

D. Ross Camidge,[1] Gregory A. Otterson,[2] Jeffrey W. Clark,[3] Sai-Hong Ignatius Ou,[4] Jared Weiss,[5] Steven Ades,[6] Umberto Conte,[7] Yiyun Tang,[8] Sherry Wang,[8] Danielle Murphy,[8] Keith D. Wilner,[8] Liza Cosca Villaruz[9]

[1]University of Colorado, Aurora, CO, USA; [2]The James Comprehensive Cancer Center, Ohio State University, Columbus, OH, USA; [3]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [4]University of California Irvine, Orange, CA, USA; [5]School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA; [6]The University of Vermont Medical Center, Burlington, VT, USA; [7]Pfizer Oncology, New York, NY, USA; [8]Pfizer Oncology, La Jolla, CA, USA; [9]Division of Hematology/Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

- MET amplification has been reported in a subset of patients with non-small cell lung cancer (NSCLC), with frequency depending on the definition used.
- Crizotinib (XALKORIR), an ALK/ROS1/MET inhibitor approved in ALK- or ROS1-positive NSCLC, has also shown clinical activity in cases of MET-amplified NSCLC.
- Preliminary analysis of a cohort of patients with MET-amplified NSCLC (N=14) enrolled in a phase 1 study of crizotinib (A8081001) was presented in 2014 using MET/CEP7 ratio cutoffs of ≥1.8–≤2.2, >2.2–<5.0 and ≥5.0 to define low, medium and high levels of MET amplification, respectively.
  - In March 2017, the MET/CEP7 ratio cutoffs for the medium and high amplification levels were revised to >2.2–<4.0 and ≥4.0, respectively, in order to enrich the high MET group with potential responders



*For 2 patients with a MET/CEP7 ratio reported as ">5.0," 5.0 was imputed as the ratio value.
†For 1 patient with a MET/CEP7 ratio reported as ">25:1," 25.0 was imputed as the ratio value.

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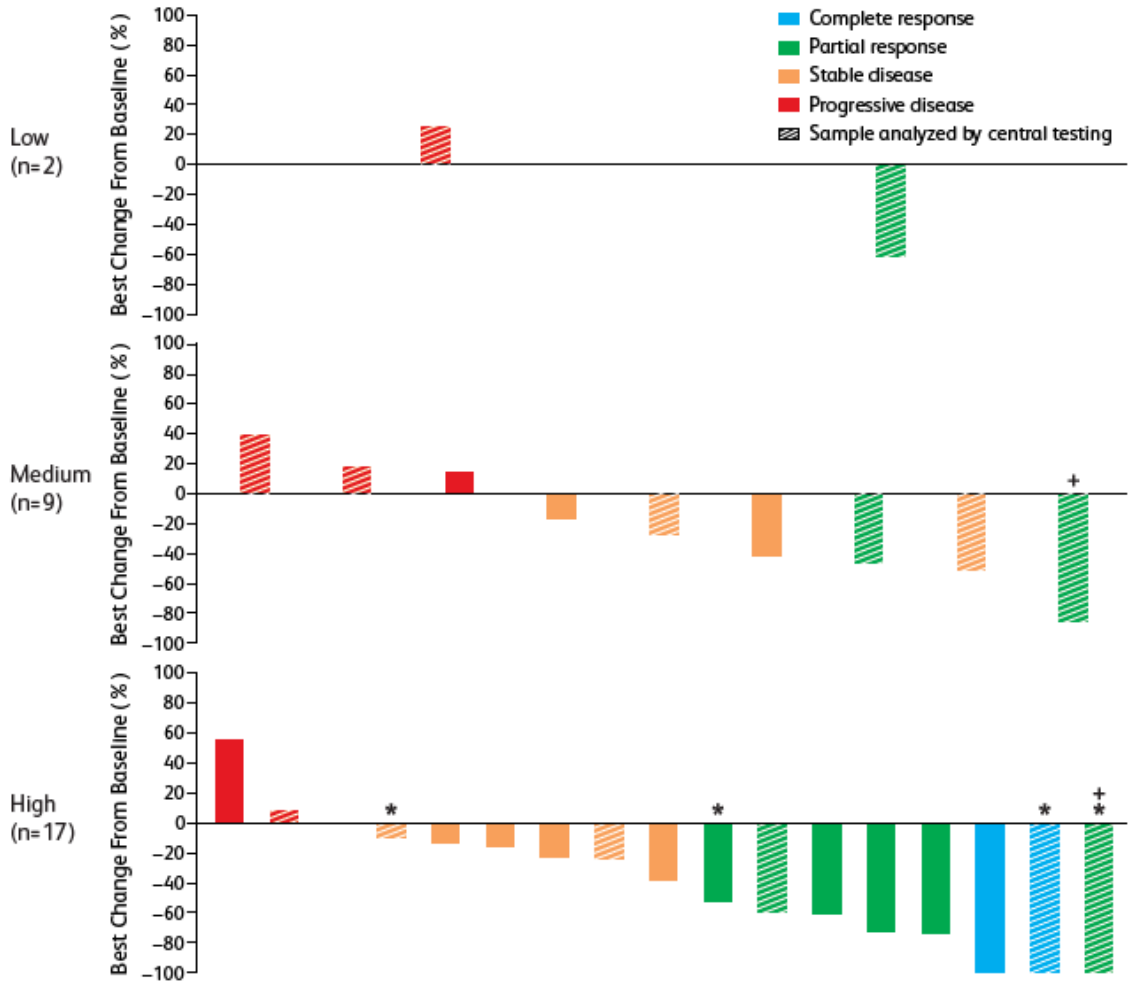
TUMOR RESPONSE IN THE RESPONSE-EVALUABLE POPULATION BY MET AMPLIFICATION GROUP

- Waterfall plot displays the best percent changes in target lesion size from baseline by derived tumor assessment in the response-evaluable population
- Tumor shrinkage was seen in all 3 MET amplification groups, and most patients in the high group had some degree of tumor shrinkage



[a]Patients reclassified from medium to high MET amplification group with MET/CEP7 ratio cutoff decrease from ≥5.0 to ≥4.0.
[b]Patients with concurrent MET exon 14 alteration.

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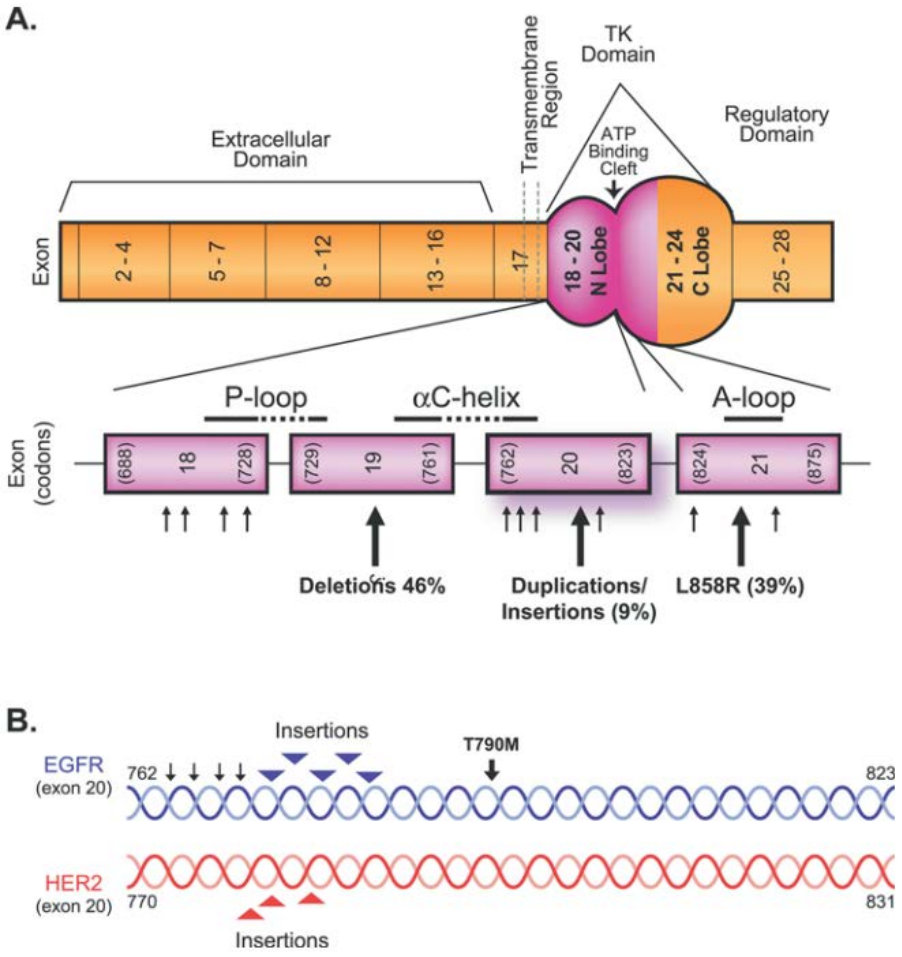
EGFR/HER2 EXON 20 INSERTIONS

- The epidermal growth factor receptor (EGFR) family is subclass I of the receptor TK superfamily, and consists of four members, **EGFR** (ErbB1), **HER2** (ErbB2), EGFR3 (ErbB3), and EGFR4 (ErbB4).



Gazdar AF, Minna JD (2005) Inhibition of *EGFR* Signaling: All Mutations Are Not Created Equal . PLoS Med 2(11): e37

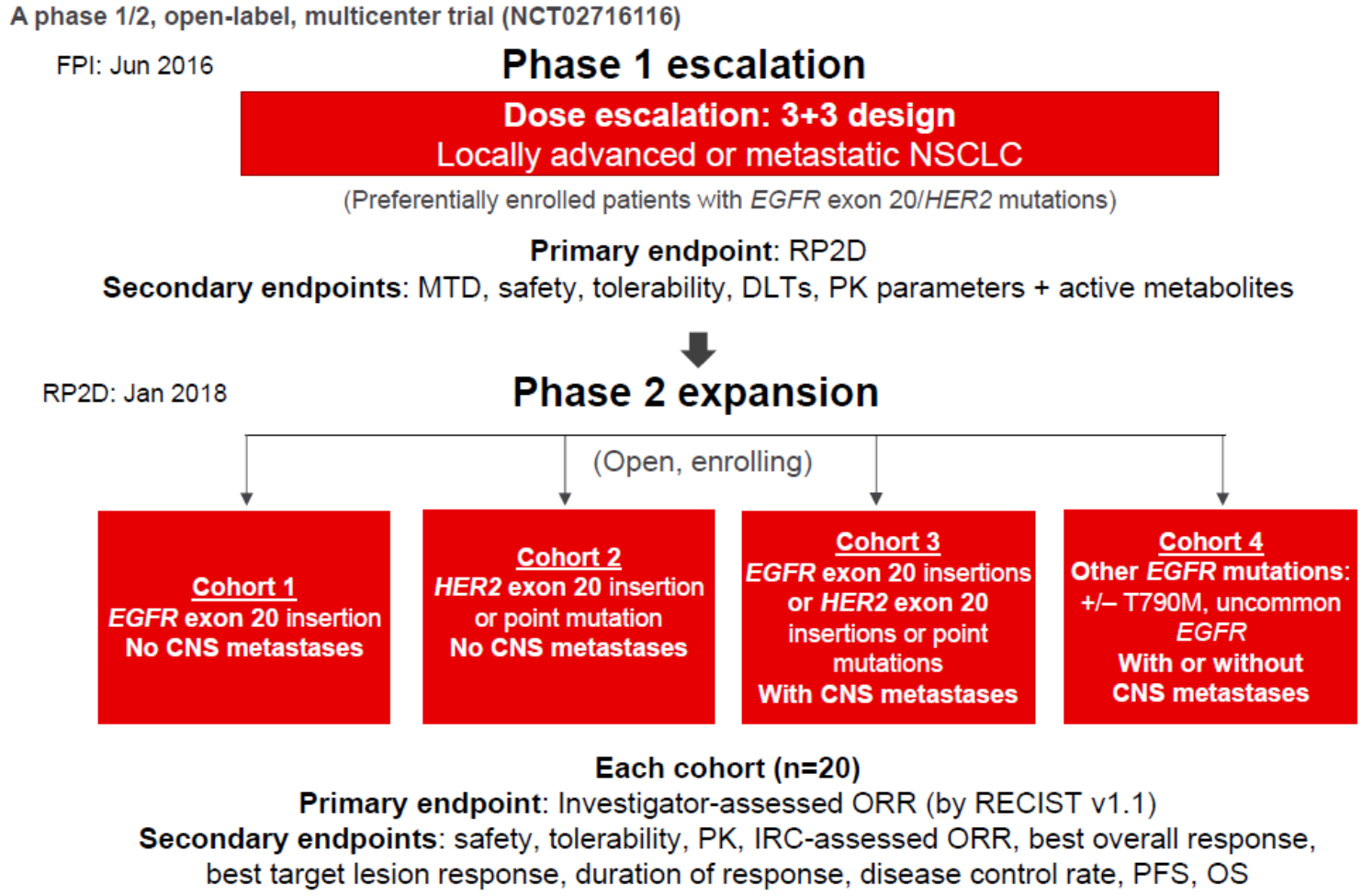
First Report of Safety, Pharmacokinetics, and Preliminary Antitumor Activity of the Oral EGFR/HER2 Exon 20 Inhibitor TAK-788 (AP32788) in Non–Small Cell Lung Cancer

Robert C Doebele,[1] Gregory J Riely,[2] Alexander Spira,[3] Leora Horn,[4] Zofia Piotrowska,[5] Daniel B Costa,[6] Joel W Neal,[7] Steven Zhang,[8] William Reichmann,[8] David Kerstein,[8] Shuanglian (Lian) Li,[8] Pasi A Jänne[9]

[1]University of Colorado Cancer Center, Aurora, CO; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Virginia Cancer Specialists, Fairfax, VA; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN; [5]Massachusetts General Hospital, Boston, MA; [6]Beth Israel Deaconess Medical Center, Boston, MA; [7]Stanford Cancer Institute, Stanford University, Stanford, CA; [8]Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [9]Dana-Farber Cancer Institute, Boston, MA

Presented at the 54th Annual Meeting of the American Society of Clinical Oncology
June 1–5, 2018; Chicago, Illinois
Poster 9015

SCHEMA OF FIRST IN HUMAN TRIAL OF ORAL TAK-788



FPI, first patient in
A Trial of AP32788 in Non-Small Cell Lung Cancer. https://clinicaltrials.gov/ct2/show/NCT02716116. Accessed Feb 16, 2018

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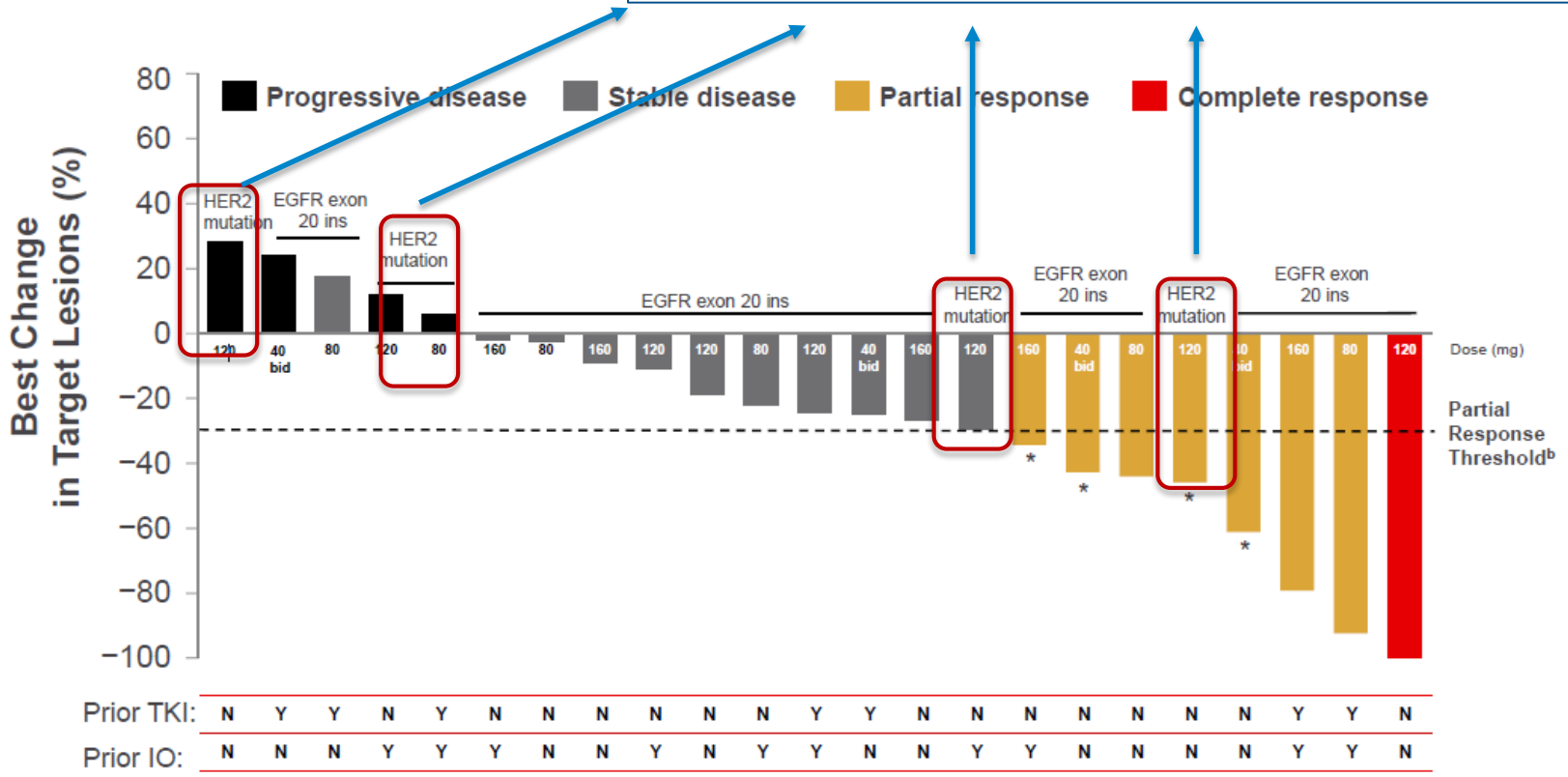
ANTITUMOR ACTIVITY OF TAK-788

One patient with a *HER2* mutation treated with 120 mg QD had a PR (awaiting confirmation)



[a] Includes 40 mg bid, 80 mg qd, 60 mg bid, 120 mg qd, and 160 mg qd dose groups
[b] Per RECIST v1.1
* Response awaiting confirmation

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The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,[1] Laetsch TW,[2] Kummar S,[3] DuBois SG,[4] Farago AF,[5] Pappo AS,[6] Demetri GD,[7] El-Deiry WS,[8] Lassen UN,[9] Dowlati A,[10] Brose MS,[11] Boni V,[12] Turpin B,[13] Nagasubramanian R,[14] Cruickshank S,[15] Cox MC,[15] Ku NC,[15] Hawkins DS,[16] Hong DS,[17] Drilon AE[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]University of Texas Southwestern, Dallas, TX; [3]Stanford University School of Medicine, Palo Alto, CA; [4]Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA; [5]Massachusetts General Hospital, Boston, MA; [6]St. Jude Children's Research Hospital, Memphis, TN; [7]Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; [8]Fox Chase Cancer Center, Philadelphia, PA; [9]Rigshospitalet, Copenhagen, Denmark; [10]UH Cleveland Medical Center, Cleveland, OH; [11]Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [12]START Madrid CIOCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; [13]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [14]Nemour's Children's Hospital, Orlando, FL; [15]Loxo Oncology, Inc., San Francisco, CA; [16]Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; [17]The University of Texas MD Anderson Cancer Center, Houston, TX

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
Hyman, LBA2501

NTRK: NEUROTROPHIC RECEPTOR TYROSINE KINASE

Neurotrophin family of receptors

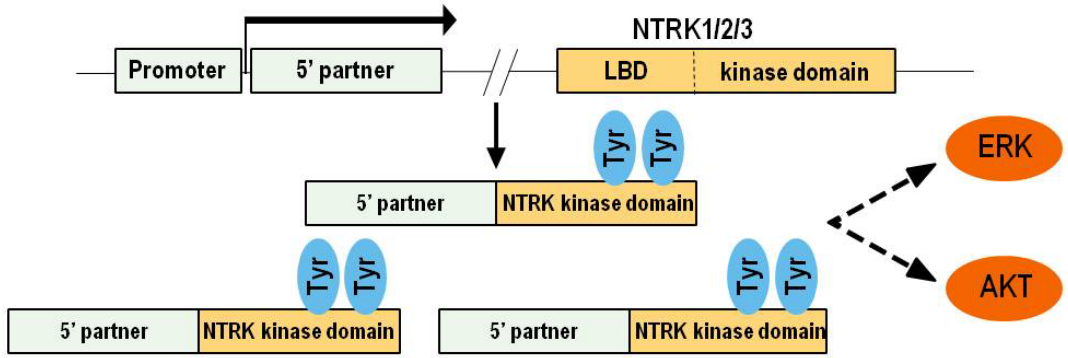
TRKA (*NTRK1*) → Pain, thermoregulation

TRKB (*NTRK2*) → Movement, memory, mood, appetite, body weight

TRKC (*NTRK3*) → Proprioception

TRK fusions

- Ligand binding domain (LBD) replaced by 5' fusion partner
- Drives overexpression and ligand-independent activation



TRK uncommonly expressed in normal tissues or cancer
Fusion drives abnormally high expression and activation of TRK kinase domain

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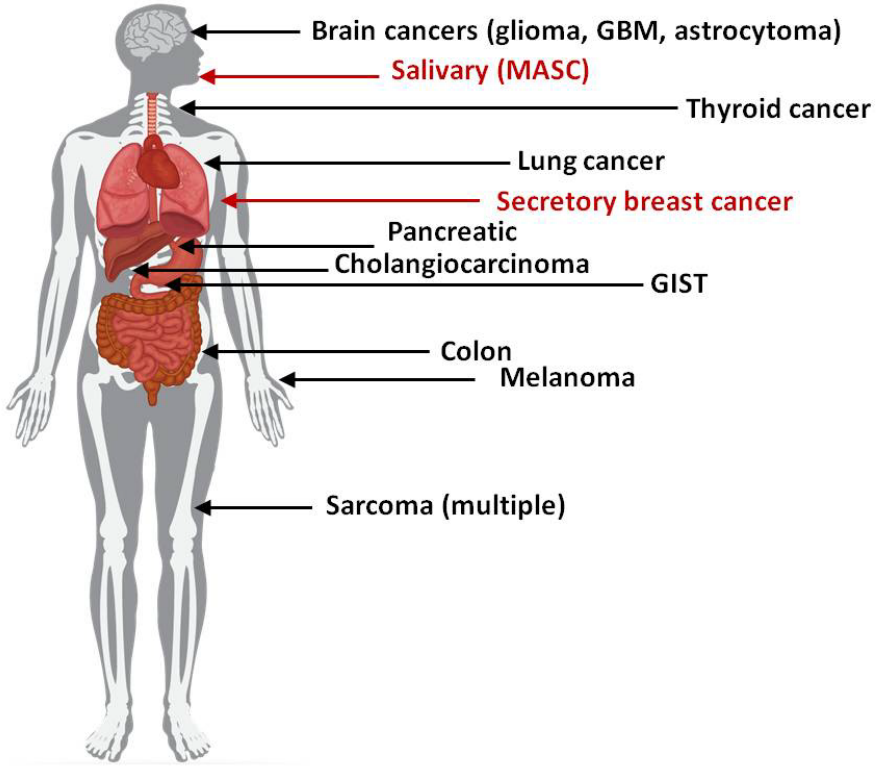
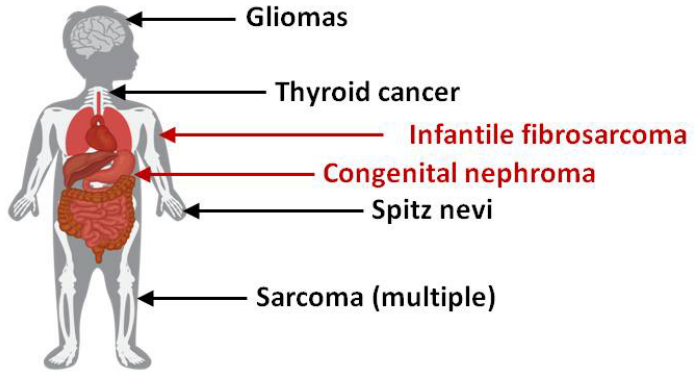
TRK FUSIONS IN CANCER



Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

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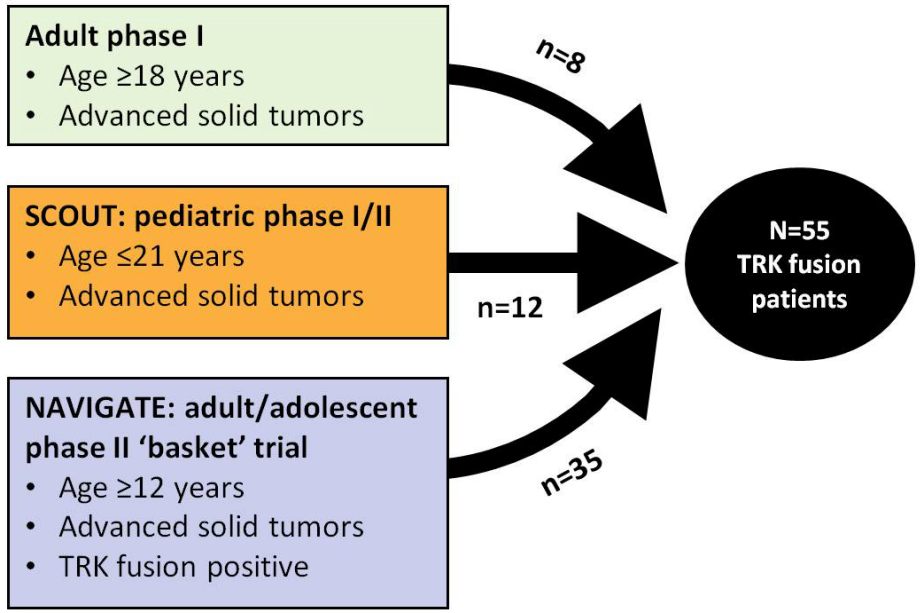
THE EFFICACY OF LAROTRECTINIB (LOXO-101), A SELECTIVE TROPOMYOSIN RECEPTOR KINASE (TRK) INHIBITOR, IN ADULT AND PEDIATRIC TRK FUSION CANCERS

Larotrectinib

- First and only selective pan-TRK inhibitor in clinical development
- Potent against TRKA, TRKB, TRKC: 5-11 nM IC_{50}

Development Timeline:

- March 2015: 1st TRK-fusion patient treated
- July 2016: Breakthrough therapy designation
- February 2017: Pivotal enrollment complete



- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment
- **Secondary endpoints**
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

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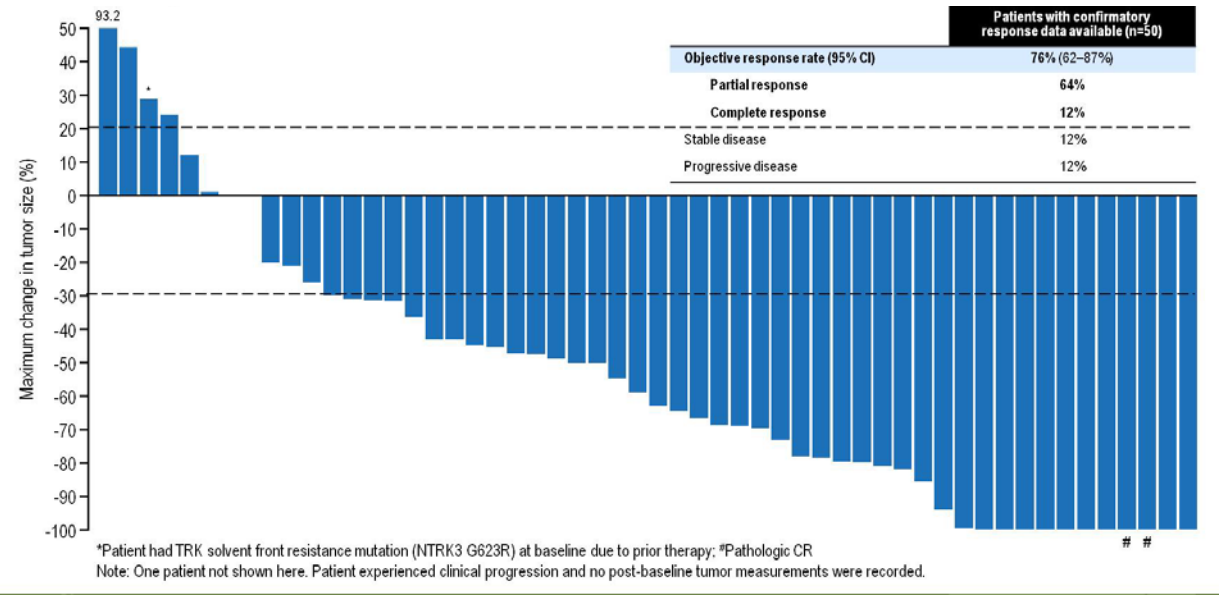
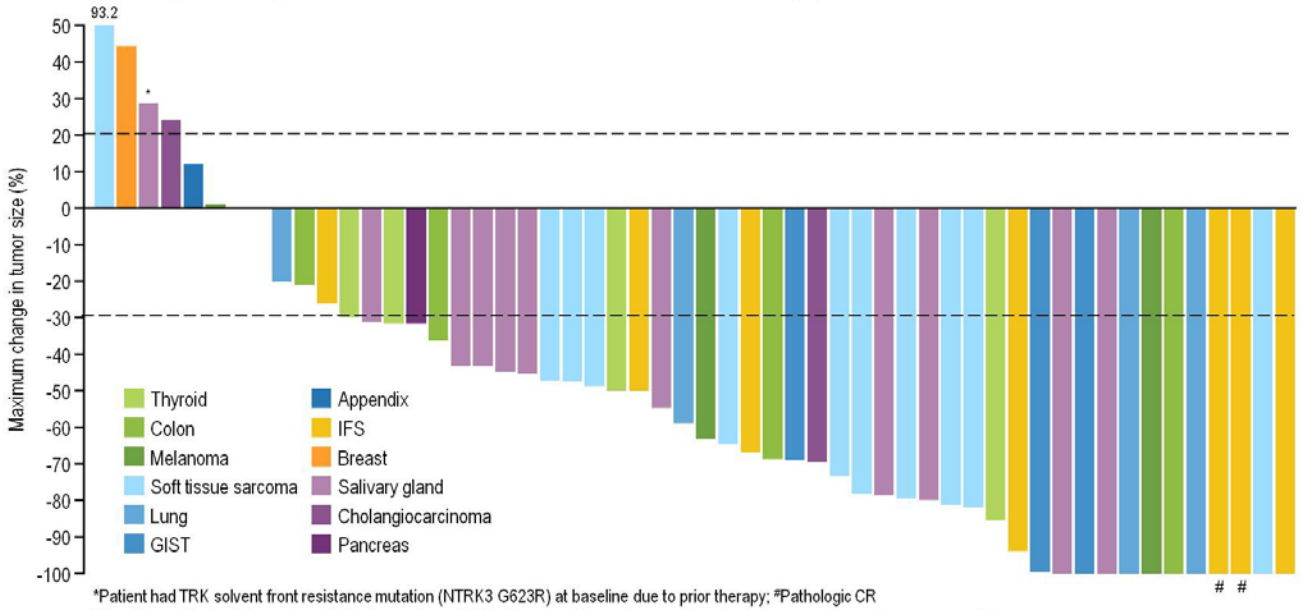
EFFICACY OF LAROTRECTINIB IN NTRK1/2/3 FUSION CANCERS



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

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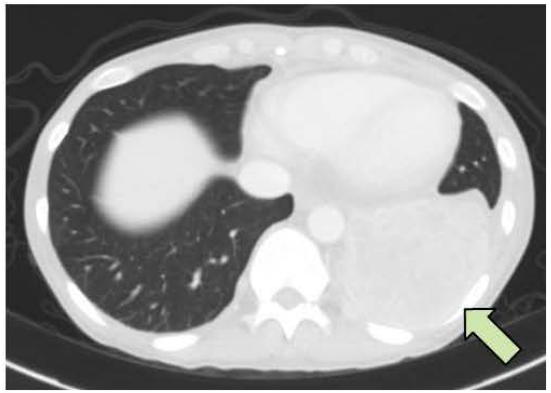
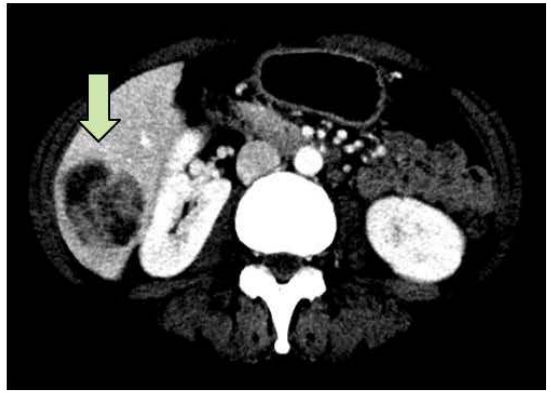
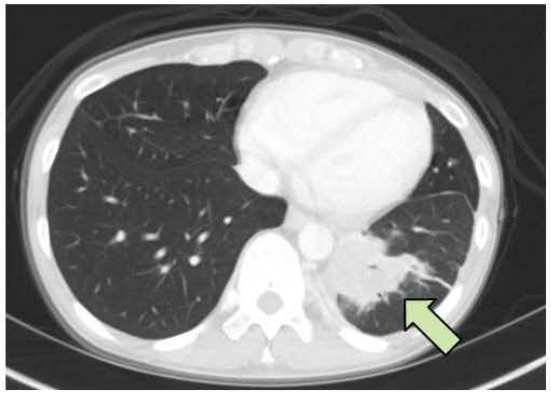
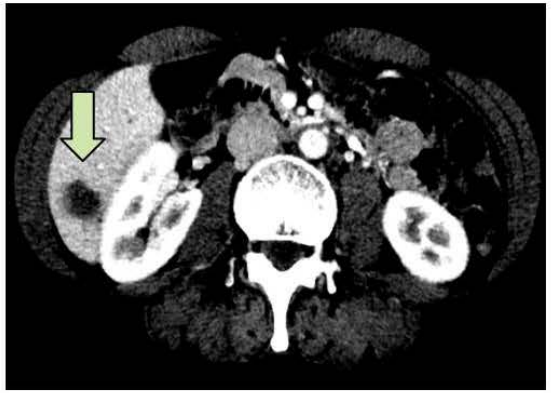
SQSTM1-NTRK1 LUNG CANCER PATIENT





Baseline





Cycle 4

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms

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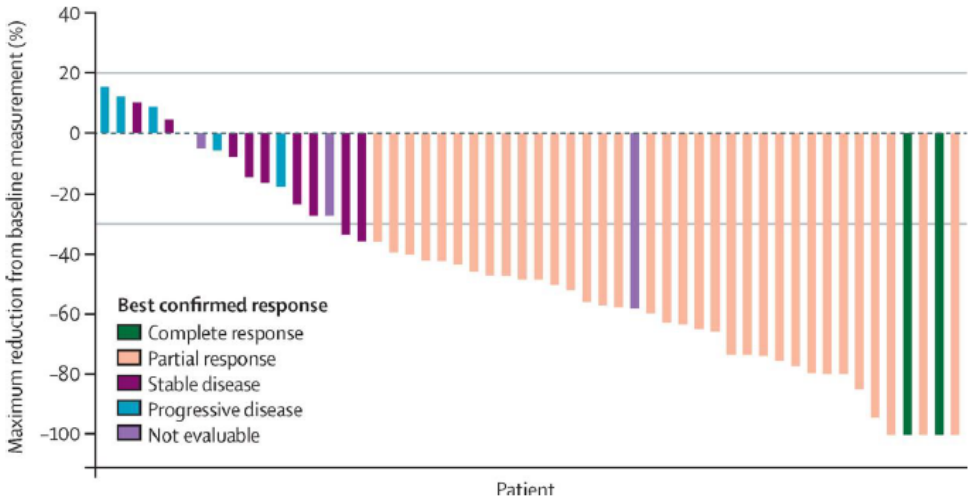
BRAF V600E

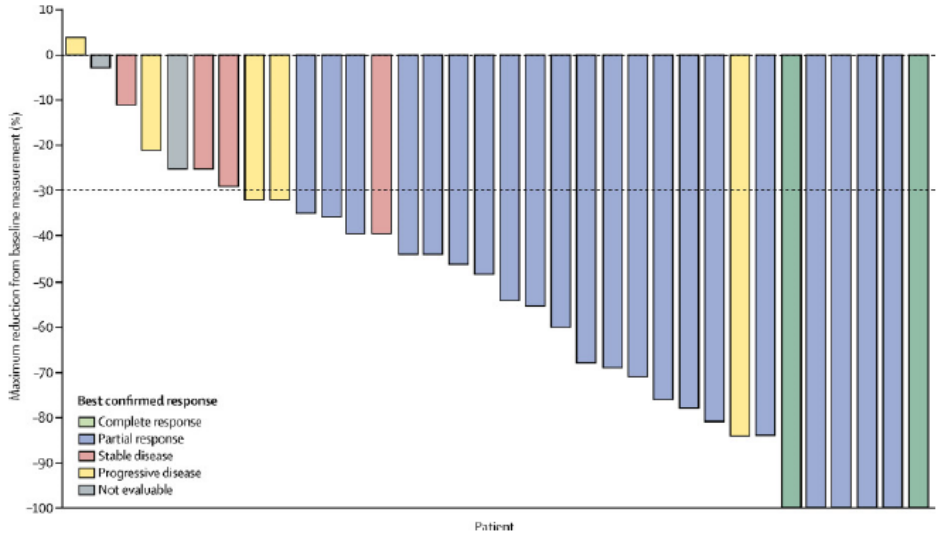
Dabrafenib/trametinib in previously treated BRAF V600E patients



ORR 63%
DCR 75.4%
mPFS 8.6 mo
(independent assessment, n=57)

Planchard et al. Lancet Oncol. 2016 Jul;17(7):984-993

Dabrafenib/trametinib in previously untreated BRAF V600E patients



ORR 64%
DCR 72%
mPFS 14.6 mo
(independent review, n=36)

Planchard et al. Lancet Oncol. 2017 Oct;18(10):1307-1316.

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Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

Julien MAZIERES, Alexander DRILON, Laurent MHANNA, Julie MILIA, Amelie LUSQUE, Alexis CORTOT, Laura MEZQUITA, Alesha THAI, Sébastien COURAUD, Remi VEILLON, Celine MASCAUX, Robert SCHOUTEN, Joel NEAL, Terry NG, Martin FRUEH, Nir PELED, Valérie GOUNANT, Sanjay POPAT, Viola ZHU, Oliver GAUTSCHI, for the IMMUNOTARGET group.

Academic Funding: Toulouse Universitary Hospital and Lucerne Cantonal Hospital

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Julien MAZIERES

1

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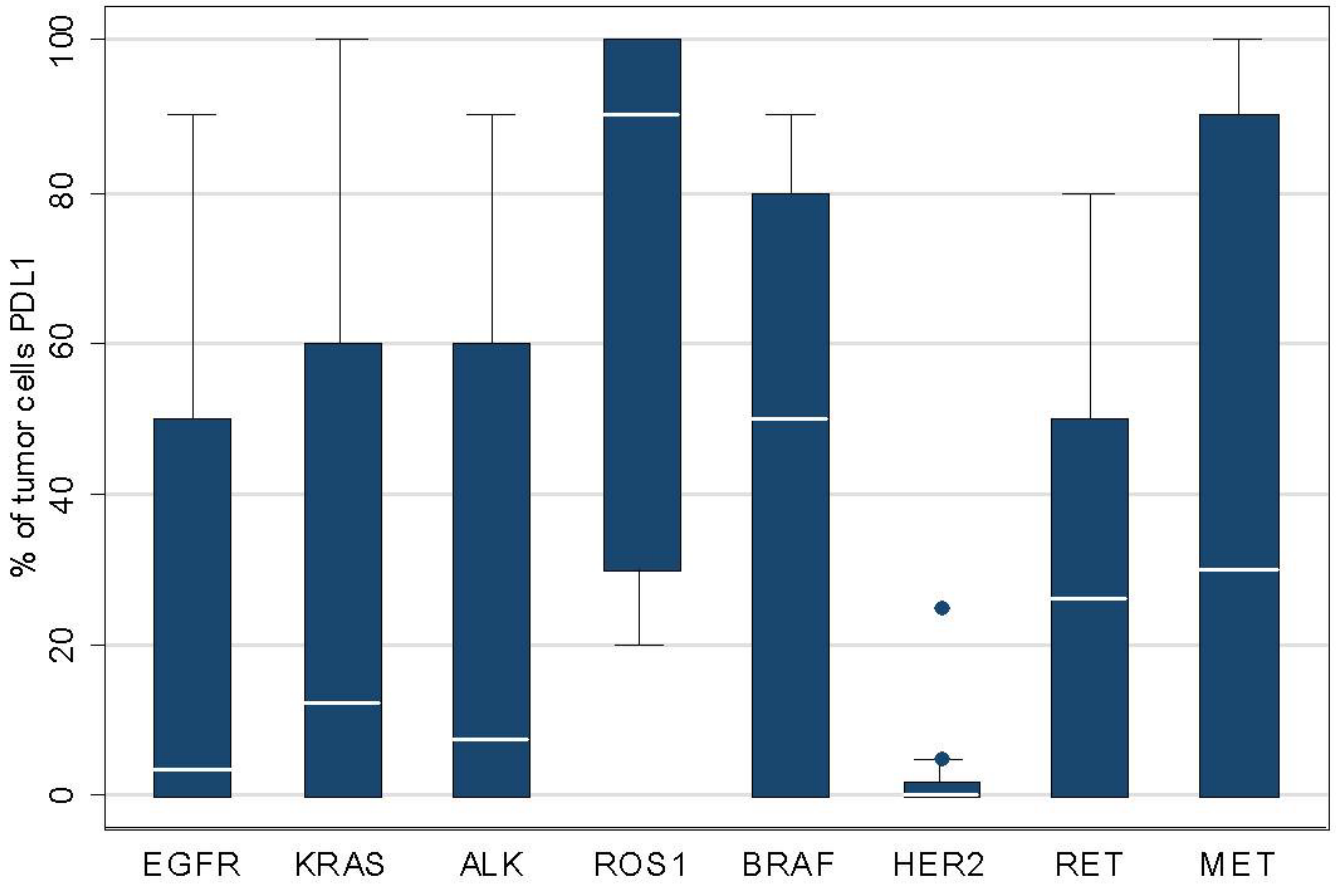
IMMUNOTARGET COHORT: PDL1 STATUS

- PDL1 expression analyzed by IHC in each center.
- Median of PDL1 expression for each driver (median and standard deviation).



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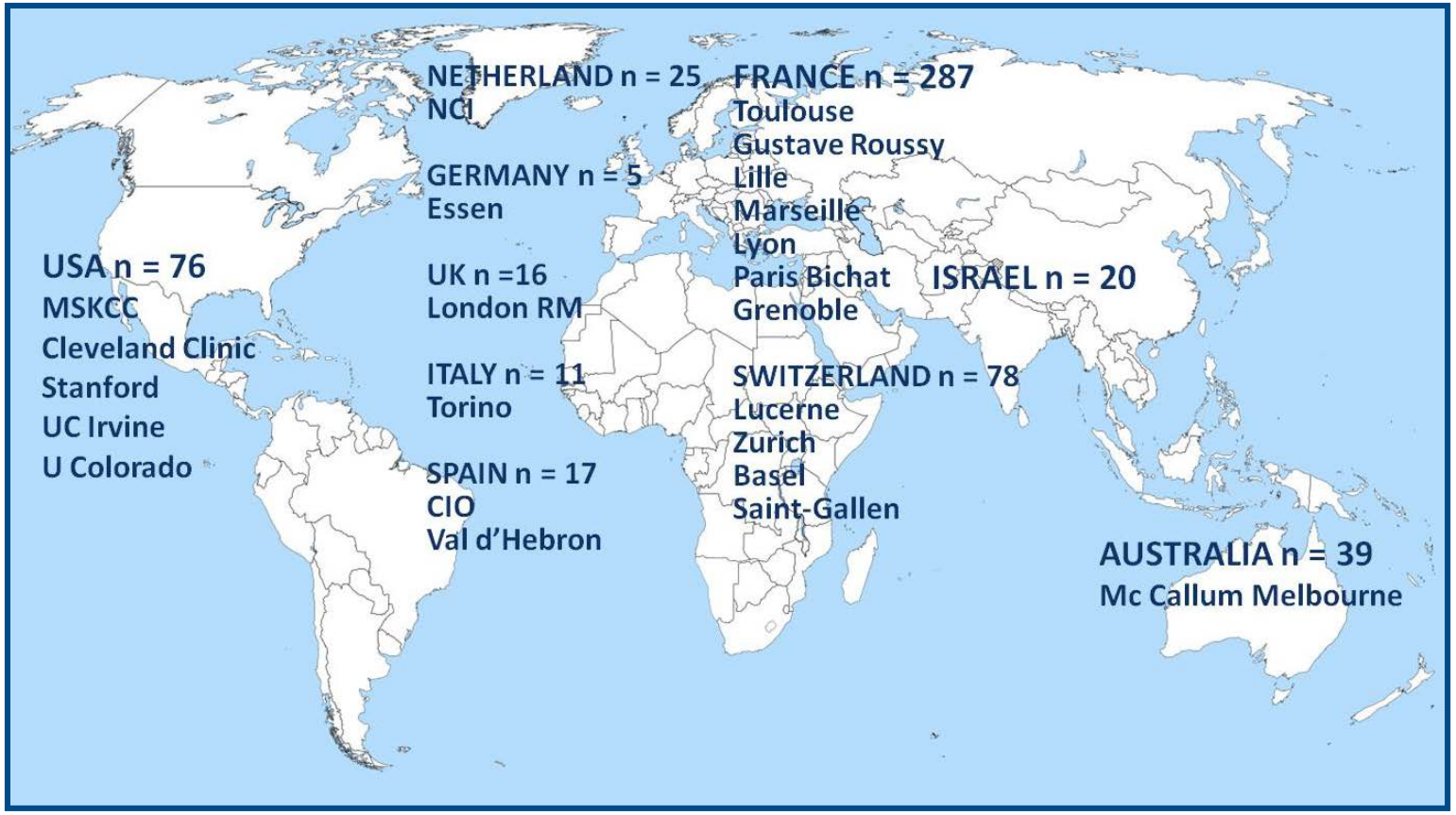
IMMUNOTARGET COHORT

- Retrospective multicenter cohort

Inclusion:

- Patients with known activating mutation
- Treated with ICI monotherapy (any line)

- **Primary objective**: PFS under ICI
- **Secondary objectives**: RR, OS, PFS ratio
- **Exploratory objective**: PDL1 expression



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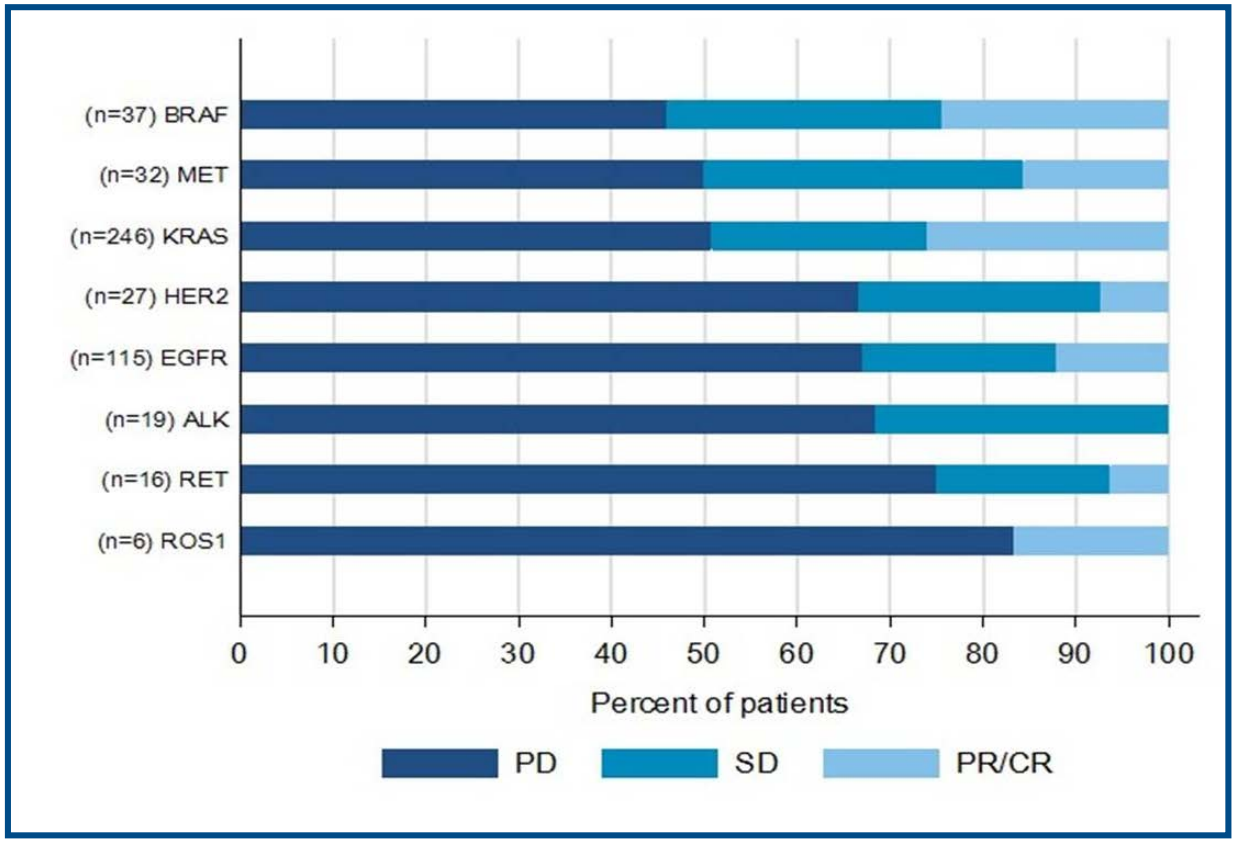
IMMUNOTARGET COHORT

Driver	PD	SD	CR/PR
BRAF	46%	30%	24%
MET	50%	34%	16%
KRAS	51%	23%	26%
HER2	67%	26%	7%
EGFR	67%	21%	12%
ALK	68%	32%	0
RET	75%	19%	6%
ROS1	83%	0	17%
TOTAL	57%	24%	19%



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CONCLUSIONS

- NGS Testing (Plasma or Tissue) increasingly recognized as important for assigning treatment options
- More therapies targeting driver oncogenes are rapidly approaching FDA approval
- Sequencing these agents with immunotherapy may be effective depending on the patient and driver oncogene but should likely be considered after conventional therapies

